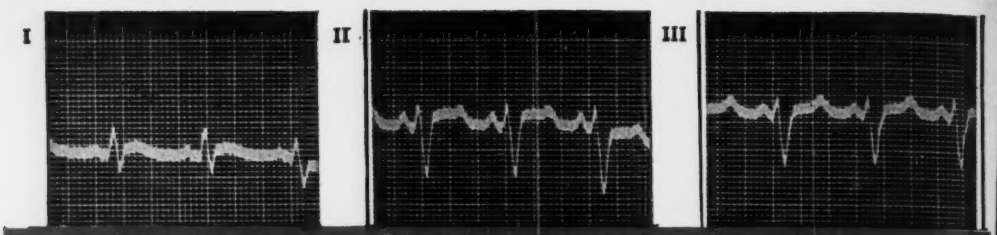
DECEMBER 1955
VOL. XII NO. 6

Circulation

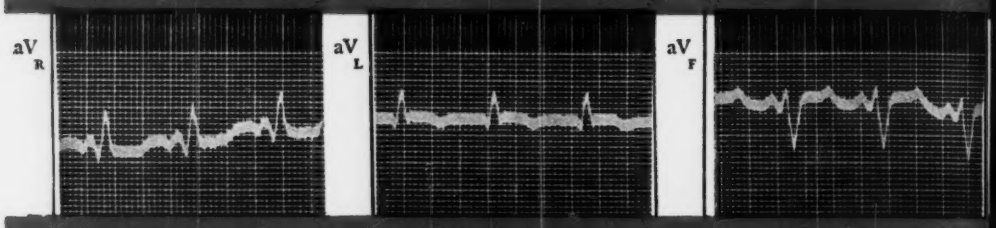
FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Published by Grune & Stratton, Inc.



REDUCE MORTALITY

in Myocardial Infarction with Severe Shock

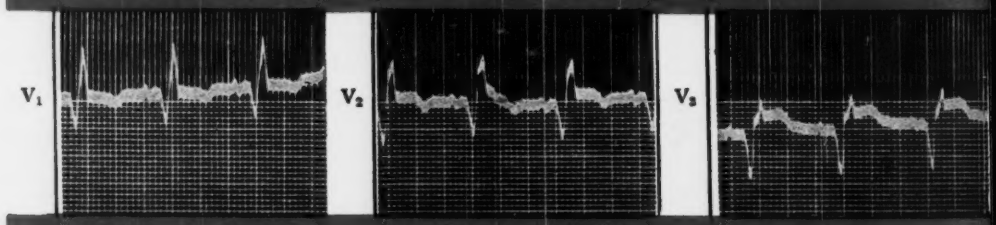


by the early use of

LEVOPHED®

BITARTRATE

the most powerful pressor antidote for shock



SUPPLIED:

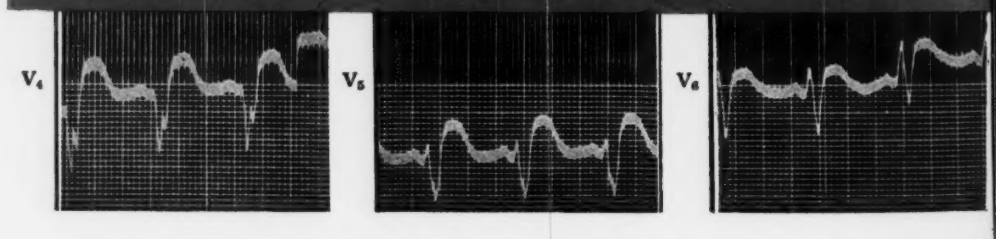
Levophed bitartrate 0.2% solution in ampuls of 4 cc., boxes of 10, to be administered in 1000 cc. of 5% dextrose solution in distilled water or 5% dextrose in saline solution.

Winthrop-Stearns INC.

New York 18, N. Y. Windsor, Ont.

Write for detailed literature.

Levophed, trademark reg. U. S. Pat. Off., brand of levarterenol



We have changed our name to

WINTHROP LABORATORIES INC.

Only the name is changed — nothing else.

Circulation

DECEMBER 1955
VOL. XII NO. 6

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

De-Epicardialization: A Simple, Effective Surgical Treatment for Angina Pectoris

By DWIGHT E. HARKEN, M.D., HARRISON BLACK, M.D., JAMES F. DICKSON, III, M.D. AND HUGH E. WILSON, III, M.D.

Removal of the epicardium of the dog's heart with 95 per cent phenol permits anastomoses between pericardial vessels and the coronary arteries that are large enough to carry the Schlesinger mass (40 micra or larger). In 18 patients suffering from intractable angina pectoris an operation consisting of phenolization, instillation of talc and pneumonopexy has resulted in consistent relief of pain. The simplicity of the procedure exposes the patient to minimum risk of fresh thrombosis; its effectiveness justifies further trial.

CORONARY insufficiency on the basis of atherosclerosis, with or without pain, is a medical problem of first importance. Medical or surgical maneuvers designed to increase the blood supply to the human myocardium will require many years for conclusive evaluation. The alleviation of pain, however, is a more immediately attainable objective. If experimental work on laboratory animals yields a safe procedure that is likely to increase the myocardial blood supply and which on conservative clinical trial relieves pain, it is worthy of further application to patients in whom pain is a dominant factor. Such a procedure is presented here.

The accumulated work in this field over the past 40 years falls into distinct patterns. Conclusions can be drawn from these that greatly simplify new work. There have been three principal approaches to the problem. The *first* is lowering of the metabolic work load. This is now accomplished by chemical rather than surgical thyroidectomy. Although proponents of this therapy can point to improvement of their cases,[10] a new disease state has been created and no favorable influence on blood supply to the myocardium can be anticipated. The *second* great field of surgical therapy for angina consists of the interruption of sensory nerve pathways. Pain can be relieved by this procedure, vasoconstriction may be reduced, and, in the combination of these effects, there may be "protection" against coronary occlusion. The *third* approach is directed at the creation of new vascular channels and has seemed most attractive to us.

From the Surgical Laboratories of the Boston City Hospital and Surgical Services of the Peter Bent Brigham Hospital, Boston, and Mt. Auburn Hospital, Cambridge, Mass.

BACKGROUND

In 1899, Francois Franck[15] first proposed sympathectomy as a surgical treatment for angina pectoris. It was not until 1916, however, that Jonnesco[17] of Bucharest actually operated on a patient with syphilitic aortitis and angina by this technic and obtained complete relief of pain. His operation consisted of bilateral extirpation of the cervical sympathetic chain and the removal of both first dorsal ganglia. Interruption of the sympathetic pain pathways has been practiced extensively throughout the intervening decades by Royle,[23] White[33] and others including ourselves.[16] Although control of pain by this means is at times dramatic, it is not consistent. Furthermore, in our experience the late mortality of 50 per cent in a

two and one-half year period after operation suggests that the progress of the primary disease had not been significantly altered.

Therefore, our interest in recent years has been in those procedures which seek to create new vascular channels to supply the myocardium. The work of Beck[1-7, 24] is preeminent among the direct attempts to improve myocardial blood supply. His early efforts were directed toward the development of vascular adhesions as a source of extrinsic coronary collateral circulation. In 1935, he used a pectoralis major muscle graft as the proposed source of new vessels with bone dust applied as an irritant after mechanical abrasion of the epicardium. Similarly, O'Shaughnessy[20] in 1936 used alleuronat paste as an irritating substance and omentum as the source of external collateral vascular supply. He presented similar experimental and clinical results. Lezius[19] in 1937 suggested lung as the source of vascularization. Various modifications of these basic recommendations have been described.[18] Outstanding among these has been the work of Thompson,[27] using talc or magnesium silicate. His clinical success has been impressive.

All of the above authors reported a strikingly similar mortality (about 70 per cent) from ligation of the anterior descending coronary artery in the unprotected dog. Fauteux[12, 13] reaffirmed this and then reported a salvage rate of 75 per cent after ligating the great cardiac vein. He modified this operation[14] in 1946 by combining pericoronary neurectomy and felt that this had further salutary protective effect.

Vineberg[29-32] since 1946 has ingeniously employed the left internal mammary artery as a source of arterial blood for the ventricular myocardium. Again, his success in protecting animals from death after ligation of the anterior descending coronary artery has been remarkably similar to that of the technique just described. Vineberg has implanted the internal mammary artery in the wall of the left ventricle and is convinced from injected and cleared specimens that new vessels branch out and communicate with the existing coronary arterial tree. Although this behavior is unlike that seen in any other part of the body, Vineberg's subsequent demonstration that the dog heart can be supplied through these anastomoses alone is quite impressive. It is still true, however, that the transplanted vessel thromboses in a significant percentage of cases and that other workers have had difficulty in repeating this work. Nevertheless this ingenious concept has had experimental support and has relieved pain in humans.

In 1948, Beck[4] first reported arterialization of the cardiac veins by producing an arterial shunt from the aorta to the coronary sinus. In a second operation, he ligated the coronary sinus between its termination in the right atrium and the anastomosis in order to effect complete reversal of flow through the coronary veins. Once again, a survival rate of approximately 75 per cent of animals, following anterior descending coronary artery ligation, was reported as well as a reduction in the size of the infarct produced. In humans suffering from angina, pain has been relieved by this procedure as well. This ambitious effort appears to have several important defects. First, it involves two major operations, one for the anastomosis and a second for ligation of the coronary sinus. This is a strenuous program for patients suffering from coronary insufficiency. Second, a number of these anastomotic shunts thrombose. Finally, if the patient does survive both of the operations and his shunt does remain patent, it is possible that high venomuroluminal shunts may enlarge and carry the blood more or less directly from the aorta into the chamber of the ventricle without being distributed to the myocardium. Furthermore, there may exist an analogy with attempts at reversal of circulation in the leg of the dog. These have clearly demonstrated that the result is commonly the same as producing a high arteriovenous fistula with a reduction, rather than increase, in the distal capillary circulation.[21] It must be conceded however, that pain is reportedly alleviated following such a procedure. Finally a serious late complication has been found by Beck's group[2] Postmortem studies have shown that atheromatous plaques have occluded the "arterialized

vascular system" suggesting that these vessels may not be able to withstand the high arterial pressures.

Again, we see substantial protection by an experimental procedure and successful human trial presented by competent observers. Yet there remains the possibility that the mechanism by which success is achieved varies from that intended. By studying these efforts at myocardial revascularization, a fascinating recurrence of experimental and clinical findings is revealed. *Over and over for the past 20 years, investigators have ligated the anterior descending coronary artery in dogs and have found that approximately 70 per cent of the normal, "unprotected" animals have died. With this base line, a wide variety of surgical procedures have been carried out on experimental animals to bring about "protection" against this fairly constant control mortality. The investigations have been associated with rather surprisingly uniform success. Not only has there been uniformity in the fact that each "protective operation" has been reported as successful by reliable investigators, but the incidence of that protection has remained the same. It is a remarkable fact that approximately 75 per cent of animals have survived ligation of the anterior descending coronary artery regardless of which of the diverse "protective" procedures was employed. Trial on humans suffering from angina has then been suggested and, generally speaking, the reports of human trial have been encouraging in terms of the relief of pain.*

The inescapable conclusion that one derives from these reports is that most of the operations are successful in a substantial number of instances and possibly, for the most part, not for the reasons put forward. It is conceivable that intrinsic coronary collaterals, as opposed to an external collateral coronary supply, have been opened. The significant increase in coronary backflow reported by Beck,[7] following a "sham operation" in which he went through all steps of his second method without permitting actual reversal of circulation to occur, supports this view.

A significant contribution in this field was that of Burchell[11] who repeated many of these technics directed at the production of vascular adhesions. He reported that small channels sufficient to carry water-soluble dyes could be produced. However, the epicardium was found to constitute a barrier that prevented the penetration of vascular channels of substantial size. The lead acetate-agar injection mass of Schlesinger which will enter only vessels 40 micra or larger in diameter did not enter the vessels produced by any of the technics tested by Burchell.

Experimental Data

It is apparent from a review of the above efforts that much work remains to be done to clarify the nature of the protective effect shared by these various techniques. The importance of hemorrhage, prolonged periods of hypotension, anoxia, even anesthesia alone in relieving angina need to be scrutinized.

The work of Burchell, however, was convincing and prompted us to investige methods of removing the epicardial barrier. At first, mechanical stripping was tried. While it is possible to remove the epicardium surgically from the normal dog's heart, this method causes such myocardial irritability and is sufficiently time consuming that is seems undesirable for application to patients suffering from extensive arteriosclerosis. In human coronary insufficiency, it seems axiomatic that direct manipulation must be as gentle and as brief as possible. It is presumed that a long operation will, per se, increase the opportunities for fall in blood pressure and tachycardia that reduce coronary flow and increase the opportunity for coronary thrombosis. Direct surgical stripping of the epicardium appeared to have both disadvantages.

Having abandoned direct surgical de-epicardialization, a variety of chemicals and irritating substances such as chlorine solutions, iodine solutions, trichloracetic acid, talc, bone dust, etc., were used. The reaction to these substances was either too violent at the time of application or too benign to destroy the epicardium. The fortunate combination of an agent that could destroy the epicardium and

yet not produce irritability during application was found in 95 per cent phenol.

Thirty-one mongrel dogs were used in phenol study. After opening the pericardium, the surface of the left ventricle was painted with 95 per cent phenol on a cotton swab. Only the left ventricle was so treated and, in order to standardize the technic, only a single application of material was employed. This resulted routinely in a graying of the epicardial surface. No alcohol was used to neutralize the phenol. In 20 of these animals Gelfoam sponges were placed over the phenolized area and the pericardium loosely closed, while in 11 one of the adjacent lobes of the lung was pulled in beneath the pericardium and sutured in this position. The results following these two slightly different modifications were essentially the same and will therefore be considered together. In all animals a strip of reactive cellophane was wrapped loosely about the origin of the anterior descending coronary artery for the purpose of producing fibrosis which would in turn reduce the calibre of the vessel and create a need for new blood supply in the area phenolized. Histologic examination of all these arteries at the time of sacrifice revealed a failure to produce the desired narrowing of the vessel and, therefore, no increased demand for new blood supply can be assumed. Whatever ingrowth of vessels was found may therefore be considered to have occurred in the absence of any ischemic stimulus.

After periods of time varying from 1 to 6 months after phenolization the surviving animals were examined in one or more of the following four ways:

(1) The chest was reopened and the adhesions to the myocardium dissected off. Both the myocardial and adhesions surfaces were then examined for evidence of arterial bleeding. In 100 per cent of animals studied in this manner three or more months after phenolization, significant arterial bleeding was noted as contrasted with none in those surviving less than three months.

(2) Survival after ligation of the anterior descending coronary artery was found to be 91 per cent, (10 out of 11) after three months; only one out of two survived before this time.

(3) Histologic examination of the hearts after phenolization revealed that the epicardium was selectively removed without damage to the underlying myocardium (fig. 1). Vessels of significant size could be found in the adhesions by this method (fig. 2) and india ink injected in these vessels revealed anastomoses with vessels within the myocardium (fig. 3).

(4) The final indication of revascularization came from injecting the agar-lead phosphate mass of Schlesinger through these new vessels. This was accomplished via the coronary system and demonstrated microscopic arterioles in the adhesions. While this injection of the adhesions establishes the fact that there

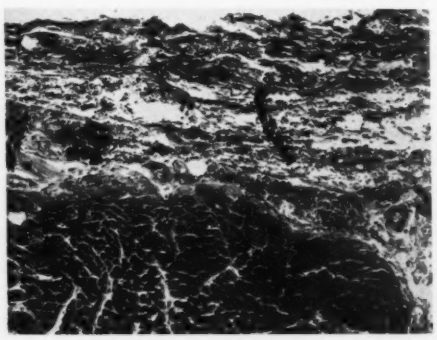


FIG. 1. Dog heart three days after application of 95 per cent phenol. Epicardium (above) is degenerating. Note lack of damage to cardiac muscle (below).

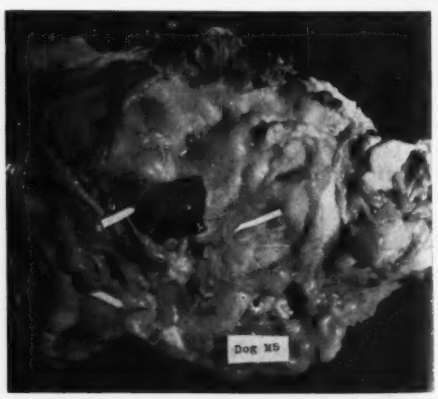


FIG. 2. Dog heart four months after phenolization. Macroscopic vessels (central arrow) between surface of heart and adhesions (right) are filled with Schlesinger mass injected into coronary artery system.

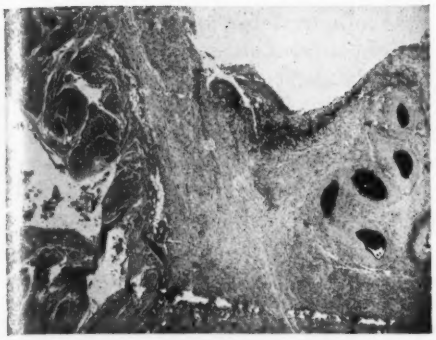


FIG. 3. Photomicrograph of dog heart showing that India ink in superficial vessels (right) enters vascular channels within the myocardium (left).

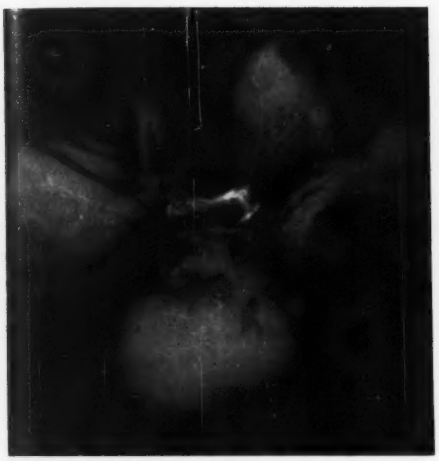


FIG. 4. Roentgenographic evidence that blood can enter the coronary system after traversing the adhesions. Isolated aorta was injected with agar-lead phosphate and this material can be seen distributed within the myocardium (below). Lungs are still attached (above).

are vessels large enough to take the Schlesinger mass, we are certainly not interested in how much blood can be supplied *to the adhesions by the coronary arteries*, but rather in how much can flow from the aorta directly into the myocardium through the adhesions. That this occurs is strongly suggested by isolating the mid-portion of the descending aorta with clamps and then injecting this segment with Schlesinger mass. The material found its way into the lungs and pericardium, thence into the myocardium through the adhesions as illustrated by roentgenograms of the myocardium after stripping away the investing structures (fig. 4).

As controls, three normal dogs that had not had the phenolization procedure had isolated aortic injection with the Schlesinger mass by an identical technique. The mass did not enter the coronary arteries. This would appear to eliminate the possibility of a false positive result in the experimental animals from previously existing collateral channels. No evidence

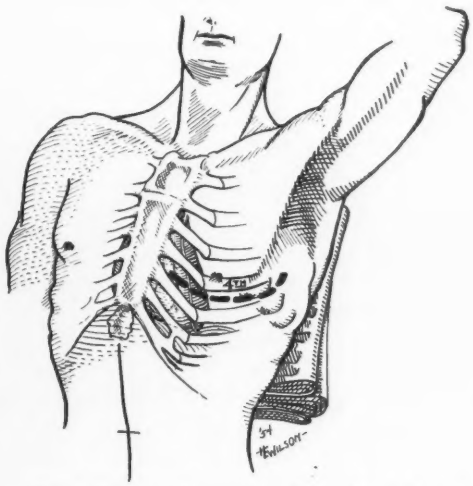


FIG. 5. Technic of operation. Patient in supine position assuring optimal ventilation. Incision is in the fourth intercostal space.

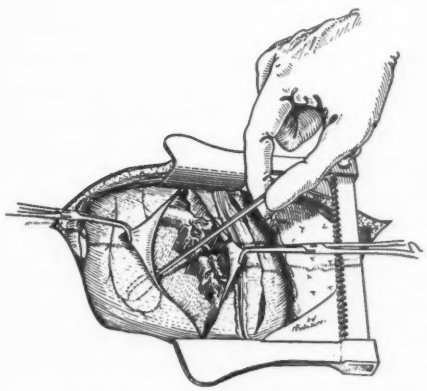


FIG. 6. Technic of operation. Pericardium opened anterior and posterior to phrenic nerve. Phenol swabbed on epicardium, avoiding coronary vessels.

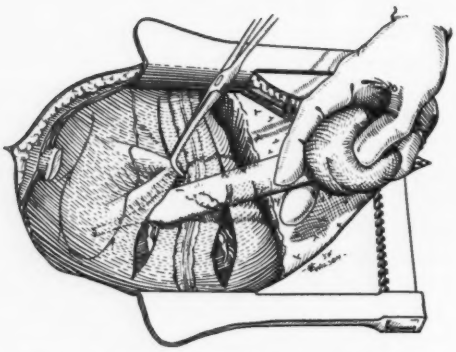


FIG. 7. Technic of operation. Powdered talc insufflated into pericardial sac.

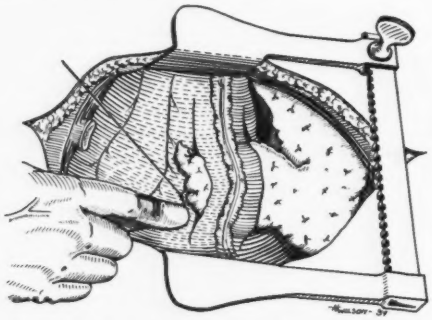


FIG. 8. Technic of operation. Lingula of lung sutured in place beneath pericardium as source of new blood supply. Pericardium left open for drainage.

of phenol toxicity was found in any of the animals.

The uniform relief of anginal pain reported following the clinical trial of the many procedures proposed elsewhere in the past for the treatment of angina pectoris fortified our hope that this extremely simple technique would also relieve pain. The experimental evidence suggested that significant extrinsic collateral blood supply might be produced and ischemia be relieved. The simplicity of this operation undoubtedly assures less risk to the patient than the more extensive procedures previously proposed.* The operation is much simpler, even, than palliatives such as denervation (figs. 5, 6). It seemed justifiable to apply the operation to a selected group of patients suffering from intractable angina. The irritating effect of powdered asbestos or talc as proposed by Beck[1] and Thompson[27] seemed a desirable addition (fig. 7). Finally, the encouraging reports of Lezius suggested the application of the lingula of the lung to the denuded myocardium as a highly vascular source of new blood supply (fig. 8).

* Total operating time in human cases has ranged from only 11 to 26 minutes.

CLINICAL APPLICATION

On Dec. 3, 1951, the first phenol de-epicardialization and pneumonopexy was performed on a 34 year old white Italian male (PBBH No. 9B755) who had had angina pectoris of severe degree for two years following an electrocardiographically-documented myocardial infarction. At the time of operation, he was having angina at bed rest. Following operation, there was a dramatic and immediate reduction in the amount of pain and almost complete disappearance within two weeks. During the next six months on restricted activity, there was occasional chest pain suggestive of angina but this was readily controlled by 2 or 3 nitroglycerine tablets a week. In less than a year, the pain had completely disappeared. The patient remains completely well except for occasional intermittent claudication which existed preoperatively and which is associated with extensive calcification of the arteries of the legs. He has been working full time for two years and has a daughter born 16 months after operation.

Seventeen additional patients have now had similar operations. All but four have had complete relief of pain; two had a recurrence of some angina about two months after operation but the pain is subsiding in one. Two patients in whom the operation has been less than completely successful have psychiatric problems that render evaluation of the real anginal residuum difficult

In these 18 patients there have been no operative deaths. Two, however, have died within two months of the operation from fresh coronary occlusion although they had been completely relieved of pain. In both instances the patients, enjoying their first respite from pain in many months, were excessively active. The experimental work would suggest that

this was before adequate collateral channels could have developed.

It is far too early to speculate about "revascularization" of the myocardium in the individuals operated on to date. However, the rather dramatic relief of pain and the simplicity of the surgery without surgical mortality suggests that it is a method worthy of continued trial.

A warning must be sounded concerning the obvious futility of attempting to improve the clinical condition of patients who have very extensive myocardial damage. It serves no useful purpose to bring a blood supply to scar. Contrariwise, no patients have been rejected from consideration for operation because of previous coronary occlusions. More than half of these patients had suffered previous myocardial infarction.

At the present time, this procedure is not being proposed for the treatment of coronary insufficiency, solely as a method of increasing coronary arterial blood flow when angina is not present. If, however, the patient has severe angina pectoris which is unresponsive to medical treatment, the operation is offered for the relief of this distressing symptom. There is reason to conclude from the experimental data and some of the longer follow-up results that a substantial improvement in coronary blood supply may also result. This experience would seem to justify the further application of this operation in human angina pectoris.

Conclusions

Some of the many surgical procedures that have been proposed for the treatment of angina pectoris have been reviewed. Most of these operations have had a remarkably similar protective effect on the survival of dogs following ligation of the anterior descending coronary artery, regardless of their nature or complexity.

The development of extrinsic collateral circulation appears to be blocked by the intact epicardium. Removal of this epicardial barrier with 95 per cent phenol has permitted the development of anastomoses with the coronary arterial tree that are large enough to carry the Schlesinger mass (40 micra or larger).

The operation of de-epicardialization, poudrage and pneumonopexy can be carried out rapidly and simply without subjecting the patient to the hazards of a fresh coronary thrombosis inherent in the more complicated operations. In 18 persons suffering from intractable angina pectoris this operation has resulted in consistent relief of pain. Further trial of this simple, clinically effective technique seems justified.

Summario in Interlingua

Es revidite alicunes del numerose procedimentos chirurgic proponite pro le tractamento de angina de pectore. Le majoritate de iste operationes ha habite remarcabilemente simile effectos protective super le superviventia de canes post ligation del descendente arteria coronari anterior, e isto in despecto del facto que il se tracta de operationes de varie typos e de varie grados de complexitate.

Le disveloppamento de un extrinsec circulation collateral es apparentemente blocate per le epicardio si isto es intacte. Le ablation de iste barriera epicardial per medio de phenol a 95 pro cento ha permittite le disveloppamento de anastomoses con le arbore del arteria coronari le quales es satis large pro portar le massa de Schlesinger (40 micros o plus).

Le operation de dis-epicardialisation, impulveramento, e pneumonopexia pote esser effectuate simple- e rapidemente sin exponer le patiente al risco de un nove thrombose como es le caso in le plus complicate operationes. In 18 patientes qui suffreva de formas intractabile de angina de pectore, iste operation ha resultate in perdurante alleviation del dolor. Essayos additional de iste simple e clinicamente efficace technica es justificate.

REFERENCES

[1] Beck, C. S.: The development of a new blood supply to the heart by operation. Ann. Surg. **102:** 801, 1935.

[2] — and Ticky, V. L.: The production of a collateral circulation to the heart. I. Experimental study. Am. Heart J. **10:** 849, 1935.

[3] —: Principles underlying the operative approach to the treatment of myocardial ischemia. Ann. Surg. **118:** 788, 1943.

[4] —, Stanton, E., Batiuchok, W. and Leiter, E.: Revascularization of the heart by graft of systemic artery into coronary sinus. J.A.M.A. **137:** 436, 1948.

[5] —: Revascularization of heart. Ann. Surg. **128:** 854, 1948.

[6] —, McAllister, F. F. and Leighninger, D.: Revascularization of heart by grafts of a systemic artery into coronary sinus. Ann. Surg. **133:** 153, 1949.

[7] — and Leighninger, D. S.: Operations for coronary artery disease. J.A.M.A. **156:** 1226, 1954.

[8] Black, H.: Discussion of restoration of coronary circulation. J. Thoracic Surg. **25:** 171, 1953.

[9] Blumgart, H. L., Schlesinger, M. J. and Zoll, P. M.: Angina pectoris, coronary failure and acute myocardial infarction. J.A.M.A. **116:** 91, 1941.

[10] —, Freedberg, A. S. and Kurland, G. S.: Treatment of incapacitated euthyroid cardiac patients with radioactive iodine. J.A.M.A. **157:** 1, 1955.

[11] Burchell, H. S.: Adjustments in coronary circulation after experimental coronary ligation with particular reference to vascularization of pericardial adhesions. Arch. Int. Med. **65:** 240, 1940.

[12] Fauteux, M.: Experimental study of the surgical treatment of coronary disease. Surg., Gynec. & Obst. **71:** 150, 1940.

[13] — and Palmer, J. H.: Treatment of angina pectoris by ligation of great cardiac vein. Canad. M. A. J. **45:** 295, 1941.

[14] —: Treatment of coronary disease with angina by pericoronary neurectomy combined with ligation of the great cardiac vein. Am. Heart J. **31:** 260, 1946.

[15] Franck, F.: Signification physiologique de la resection du sympathique dans la maladie de baseton, l'epilepsie, l'idistre et le glaucome. Bull. Acad. de Méd., Paris. **41:** 594, 1899.

[16] Harken, D. E., Farrand, R. E., and Norman, L. R.: Surgical management of anginal pain. Proc. New England Cardiovasc. Soc., 1949–1950, p. 29–31.

[17] Jonnesco, T.: Traitement chirurgical de l'angine de poitrine par la resection du sympathique cervico-thoracique. Bull. Acad. de méd., Paris **84:** 93, 1920.

[18] Key, J. A., Kergin, F. A., Martineau, Y. and Leckey, R. C.: A method of supplementing the coronary circulation by a jejunal pedicle graft. J. Thoracic Surg. **28:** 310, 1954.

[19] Lezius, A.: Die anatomischen und funktionellen Grundlagen der künstlichen Blutversorgung des Herzmuskels durch die Lungen bei Coronarterien Verschluss. Arch. f. klin. Chir. **191:** 101, 1938.

[20] O'Shaughnessy, L. O.: An experimental method for providing a collateral circulation to the heart. Brit. J. Surg. **23:** 665, 1936.

[21] Palmer, T. H. and Welch, C. S.: Experimental studies on reversal. of the circulation in the lower extremity. Surg., Gynec. & Obst. **94:** 206, 1952.

[22] Beck, C. S.: Personal Communication.

[23] Royle, N. D.: Observations on the alteration of circulation to the brain by surgical means in diseases of the central nervous system. Brit. M. J. **1:** 1063, 1932.

[24] Schildt, P., Stanton, E. and Beck, C. S.: Communications between coronary arteries produced by the application of inflammatory agents to the surfaces of the heart. Ann. Surg. **118:** 34, 1943.

[25] Schlesinger, M. J.: An injection plus dissection study of coronary artery occlusions and anastomoses. Am. Heart J. **15:** 528, 1938.

[26] Schlesinger, M. J. and Zoll, P. M.: Incidence and localization of coronary artery occlusions. Arch. Path. **32:** 178, 1941.

[27] Thompson, S. A. and Plachta, A.: Fourteen years experience with cardiopexy in the treatment of coronary artery disease. J. Thoracic Surg. **27:** 64, 1954.

[28] Thorel, C.: Pathologie der Kreislauforgane. Ergebn. d. allg. Path. u. path. Anat. **91:** 559, 1903.

[29] Vineberg, A. M.: Development of anastomoses between coronary vessels and transplanted internal mammary artery. Canad. M. A. J. **55:** 117, 1946.

[30] — and Jewett, B. L.: Development of an anastomosis between the coronary vessels and a transplanted internal mammary artery. Canad. M. A. J. **56:** 609, 1947.

[31] —: Treatment of coronary artery insufficiency by implantation of the internal mammary artery into the left ventricular myocardium. J. Thoracic Surg. **23:** 42, 1952.

[32] — and Buller, W.: Pericardial fat blanket to supplement internal mammary artery implant. Canad. M. A. J. **70:** 76, 1954.

[33] White, J. C., Smithwick, R. H. and Simeone, F. A.: The Autonomic Nervous System. Ed. 3, New York, Macmillan, 1952.

The Changes in the Intra-Arterial Pressure during Immersion of the Hand in Ice-Cold Water

By JOHN O. GODDEN, M.D., GRACE M. ROTH, PH.D. AND EDGAR A. HINES, JR., M.D.

With the Technical Assistance of Jerry F. Schlegel, B.S.

The response of the intra-arterial pressure to the cold immersion stimulus was studied in 42 healthy young adults, continuous direct (arterial-pressure) recording being used. The average systolic elevation was 22.6 mm. Hg and the average diastolic elevation was 16.3 mm. Hg. The difference between direct and indirect methods of measuring blood pressure was studied in 351 simultaneous determinations in 35 of these young adults. The direct systolic pressure averaged 9.7 mm. Hg higher and the diastolic pressure was 7.3 mm. Hg lower than the indirect measurement.

THE cold pressor test of Hines and Brown[1] has been used widely during the past 22 years in the study of essential hypertension[2-9] and the toxemias of pregnancy.[10, 11] Up to the present, exact knowledge of the nature and significance of the cold pressor response has been limited by the intermittent measurements possible with the sphygmomanometer. However, now that continuous direct recording of arterial pressure is established as an accurate and reliable laboratory procedure, a new tool is available for the study of the cold pressor test.

The response of the intra-arterial pressure to the cold immersion stimulus (4 C. for 60 seconds) was studied in 42 healthy young adults, continuous direct arterial pressure recording being used. The cold pressor test of Hines and Brown was applied repeatedly at short intervals, and the direct record was examined with regard to (1) maximal elevation of pressure, (2) time required to reach the maximal pressure and (3) time needed to return to one half the maximal pressure (the last figure was taken as a measure of the recovery time). The difference between the direct and indirect methods of measuring blood pressure was studied in 351 simultaneous determinations in 35 of these young adults.

From the Mayo Clinic and Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Abridgment of the thesis submitted by Dr. Godden to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

HISTORY OF THE COLD PRESSOR TEST

In 1932, Hines and Brown[1] described an icewater immersion test (the cold pressor test) designed to measure individual vascular reactivity. Many methods of stimulation, including electric shocks, loud noise, bright lights and the inflicting of pain, had been tried previously. However, none of these stimuli gave consistent results when repeated in the same individual. Hines, working with the late Dr. G. E. Brown, had observed that a patient with cold sensitivity responded with a marked elevation of blood pressure when an extremity was immersed in ice water. The development and application of this cold pressor test are described in the following papers.[1, 4-8] The test has been used since by others,[3, 9-11] chiefly in the investigation of essential hypertension and toxemia of pregnancy.

By 1940, Hines[7] had applied this test approximately 5,000 times in 1,856 persons, of whom 1,015 had a usually normal blood pressure and 841 had essential hypertension. In the entire group with a usually normal blood pressure, the mean increase was 16.2 mm. Hg for the systolic pressure, and 13.2 mm. for the diastolic. The group with a usually normal blood pressure was divided into hyporeactors and hyperreactors on the basis of a rise less than, or more than, 20 mm. of mercury in systolic and 15 mm. in diastolic blood pressure. Approximately 85 per cent of subjects with usually normal blood pressure fell in the group of hyporeactors. In 1951, Hines[8] revised his limits of normal vascular reactivity to define normoreactors as those having a diastolic elevation between 10 and 20 mm. Hg.

The cold pressor test rests on certain assumptions regarding the physiology of the cardiovascular

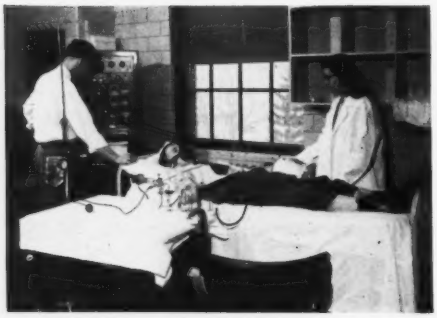


FIG. 1. A subject, with the intra-arterial needle in place, during a direct arterial-pressure recording.

system. Some of these assumptions are as follows:

(1) The individual response to the cold stimulation, applied exactly as described by Hines, is constant to a degree suitable for use as a clinical test (±10 mm. Hg).

(2) Rapid elevations of blood pressure, unassociated with cardiac acceleration or increased cardiac output, are brought about by vasoconstriction which produces a sudden increase in peripheral resistance.

(3) This test is a measure of vasoconstrictor response. The diastolic elevation to the stimulus is a more reliable index of vasoconstriction than the systolic increase.

(4) The cold pressor test is an index of vascular (vasoconstrictor) reactivity.

There is, to our knowledge, no literature on the response of the intra-arterial pressure to cold stimulation either in health or in disease. Hines and Brown[4] reported, from their studies using indirect measurement of blood pressure, that a sustained increase in the cold pressor response is seen only in persons with essential hypertension.

This study investigates the response of intra-arterial blood pressure in 42 adult human subjects to a standard cold stimulus (the cold pressor test). A continuous record was made of the beat-to-beat changes in arterial blood pressure in 42 healthy young adults. The primary purpose in this project was to study the intra-arterial pressure response to cold immersion with a newer and more accurate technic. This approach studies the total cardiovascular response as expressed in peripheral arterial pressure to a powerful stimulus.

METHODS AND PROCEDURE IN THIS STUDY

The group of 42 healthy young adults who cooperated in this project was unselected in any way, except that any person having a history or physical findings suggestive of cardiovascular or renal disease was excluded from the project. The women were young student nurses, all subject to pretraining and, thereafter, annual physical examinations. The men were either student nurses, hospital orderlies or graduate physicians. The population of the project is weighted in favor of young female subjects, the majority having "low normal" blood pressures. No selection was made on the basis of the response of the individual to the cold pressor test.

Casual indirect blood-pressure readings obtained from the young adults used in this project were reviewed in respect to the new standards of normal blood pressure proposed by Master and associates.[12] Almost 300 indirect measurements were made and in only two isolated estimations were these limits exceeded at either the systolic or diastolic levels. Two female subjects had indirect blood-pressure determinations on one occasion of 130/90 and 120/86 respectively. The limit of normal pressure for this age group of Master and associates was 130/85.

Intra-arterial pressure was conducted through the radial needle up a saline-filled polyethylene tube to the strain gauge (fig. 1). This instrument converts the mechanical thrust of blood pressure into electric energy, which moves the stylus of the recroder. A wash bottle filled with heparinized saline solution, joined in parallel with the strain gauge, allows the radial needle to be flushed out by adjusting the three-way stopcock. The flushing of the adial needle with saline solution has no discernible effect on the intra-arterial pressure, except that it obliterates the direct record for three to five pressure pulses. An aneroid manometer was used to keep the pressure in the system above arterial pressure at all times. An ice bucket, thermometer and blood-pressure cuff needed for the cold pressor test completed the equipment.

A Sanborn polyviso multichannel recorder was used, inscribing simultaneously (1) the electrocardiogram, (2) respiratory excursions and (3) direct arterial pressure. Two Statham strain-gauge manometers of different sensitivities were needed for respiratory (10.4 pounds per square inch) and circulatory (0 to 15 pounds per square inch) pressures. (Both can be seen in fig. 2; the pulmonary strain gage lying beside the pillow is concealed by the wash bottle in fig. 1.) The method of using this equipment has been described by Wood, Lambert and Burchell.[13, 14] The same equipment was used and the same technic was followed throughout the project unless otherwise noted.

The Sanborn recorder was allowed to "warm up" for 20 to 30 minutes. Each stylus had been tested for sensitivity and adjusted if necessary. The stylus recording arterial pressure was calibrated against an aneroid manometer* through the range expected in the individual subject, that is, from the lowest diastolic pressure at rest to the highest systolic

* This instrument has been checked repeatedly with a mercury manometer, which is the permanent standard in the cardiac-catheterization laboratory of this institution.

pressure obtained during cold stimulation. This calibration was inscribed stepwise in increments of 20 mm. Hg at the beginning and end of each record. It was later used to derive a scale card for the measurement of the individual pulse wave in millimeters of mercury.

Each radial puncture produced a continuous record of the intra-arterial pressure during the performance of three or more cold pressor tests which were preceded, separated and followed by 15-minute rest periods. The record contained the individual's response, by blood-pressure alteration, to three or more severe stress situations (fig. 3). The records were later studied with regard to (1) basal pressure, (2) maximal pressure obtained as a result of stimulation, (3) time elapsed from stimulation to maximal elevation in pressure and (4) time from stimulation to one-half maximal pressure after cessation of stimulus.

A continuous electrocardiographic tracing was made throughout the direct arterial-pressure recording, standard lead II being used. A short record of the standard leads I, II and III and the three unipolar limb leads aV_R, aV_L and aV_F was included at the end of the tracing. The individual QRS deflections were discernible even at slow paper speeds.

A continuous record of the respiratory cycle was made, an oxygen mask connected to a pressure manometer being used. A large rounded wave of good amplitude was recorded in response to the pressure changes at the oral end of the airway. This record gave reliable evidence of the quality of the subject's steady state. The details of the technic for recording the individual direct pressure tracing were largely empirical during the early stages of this project. There were two limiting factors, the duration of the steady state under the conditions required for direct recording, and the time required for the subject to recover from the effects of a powerful vasomotor stimulus. A trial, reported below, was made during which 10 young adults were subjected to five cold pressor tests, at 15-minute intervals. The results of this exercise enabled us to adopt two postulates: (1) The subject could tolerate the radial needle and the discomfort of repeated cold immersions for at least one hour. (2) There was no significant difference between repeated cold pressor tests.

A standard one-hour procedure was subsequently adopted in which three cold pressor tests were carried out at 15-minute intervals. The individual cold pressor tests in our project were recorded at either 5 mm. per second or 25 mm. per second paper speeds. The same speed was used for the basal period (20 seconds before immersion), for the minute during immersion and for a period of 30 seconds after withdrawal of the stimulus. All resting periods were recorded at a speed of 1 mm. per second, which allowed continuity to be maintained with a minimal expenditure of record paper.

FIG. 2. The application of the cold immersion stimulus. A technician (right) is immersing the subject's hand and wrist in ice water. Another technician is observing the effect on the arterial-pressure tracing.

The shape of the pressure pulse was frequently altered by reflected waves which appeared on the descending limb of the pulse wave, either distorting the dicrotic notch or separate from it. These reflected waves, which are agreed to be evidence of increased peripheral vasoconstriction, were followed at rapid paper speeds until they disappeared from the record. They persisted, in some cases, for several minutes, passing away as the blood pressure declined toward basal levels.

INTERPRETATION OF THE DIRECT TRACINGS

The response of the channel of the Sanborn unit which recorded arterial pressure was calibrated, as previously described, through the expected maximal range from the lowest diastolic to the highest systolic pressure before and after each individual procedure. A scale card was constructed from these calibrations which measured the amplitude of the pressure pulses directly in millimeters of mercury (the white rectangle at the left margin of fig. 3). The definition of certain terms used in reporting the results of this study follows:

(1) The basal pressure, systolic and diastolic, is defined as the average of all appropriate pressure pulses in the 20-second period just before immersion. The basal pressure was taken in the period immediately before the application of the cold stimulus in order to cancel out, as far as possible, any rise in blood pressure due to other causes.

(2) The maximal pressure given is the value, in millimeters of mercury, of the pulse wave of greatest amplitude occurring during or after

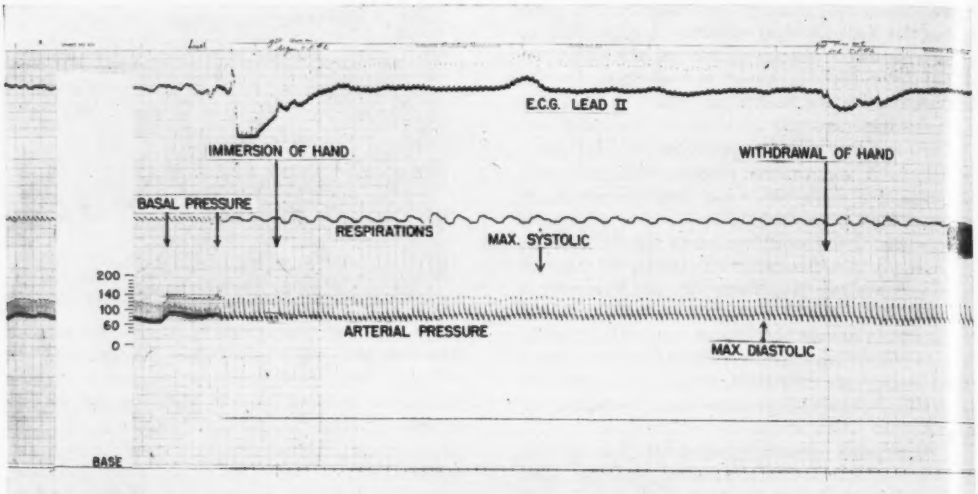


FIG. 3. A section of a typical direct recording showing the response of the arterial pressure to immersion of the hand in cold water (direct arterial pressure is the lowest tracing with the calibration in millimeters of mercury on the extreme left).

cold immersion. Pressure pulses rising abruptly above the general level of their contemporary pulse waves and those occurring immediately after release of the blood-pressure cuff were not used. The common artifacts in the tracings were due to the brief obliteration of the pulse wave during simultaneous use of the blood-pressure cuff and, in one case, to the occasional occurrence of cardiac extrasystoles.

(3) One-half maximal pressure is the value, in millimeters of mercury, of the first pressure pulse, occurring after maximal elevation has been attained, having an amplitude midway between that of the basal and maximal pulse waves. This value can be determined by simple arithmetic without scanning the postwithdrawal segment of the direct record. However, the time of occurrence of this pressure was considered to be important in this project.

(4) The time to maximal pressure and the time to half-maximal pressure are the intervals measured in seconds from the immersion of the hand in ice water to the occurrence of the appropriate pulse wave.

There are three groups of normal subjects. These groups are cumulative, that is, group I forms part of group II and group III takes in all normal subjects. Group I: 10 subject each having five consecutive tests; Group II: 36 subjects each with three tests and Group III: 42 subjects with a total of 136 tests.

Initially, 10 healthy young adults were subjected to five consecutive cold pressor tests at 15-minute intervals to study the consistency of response in repeated tests. Then, an additional 26 young adults had three consecutive cold pressor tests at the same interval. These individuals and those in group I make up the 36 subjects in group II. These two groups are reported together and compared in various ways later in the paper. Finally, the data from 136 cold pressor tests in 42 young adults were combined and examined as 136 individual tests.

A comparison of direct and indirect blood-pressure determinations was made in 35 of the 42 healthy young adults taking part in this project.

A preliminary study was made to determine the time needed for return to resting blood pressure between repeated cold pressor tests.

A group of 10 healthy young adults was studied, during the design of the project, to determine the consistency of the individual response to repeated immersion stimuli. It was important to learn if the subject retained his ability to respond maximally when the

stimuli were applied at short (15-minute) intervals, inasmuch as no information was available regarding the time needed for recovery after the cold pressor test.

Ten young adults, six men ranging from 20 to 26 years of age (average 22 years) and four women, all 20 years of age, were each subjected to five cold pressor tests at 15-minute intervals. The mean elevations in arterial pressure of each series of tests (test 1 in 10 subjects, and so forth) were examined statistically for the significance of differences between consecutive tests. These differences of means, 10 systolic and 10 diastolic pairs in their various combinations, when compared, showed that the differences of two systolic pairs, tests 1 and 2 and tests 1 and 3, had borderline significance but, in the small sample examined, there was no significant difference in the diastolic responses. Tables 1 and 2 contain the results of this preliminary study. The data for five consecutive cold pressor tests in 10 young adults are in the upper row of figures for tests 1, 2 and 3 and are the only figures presented for tests 4 and 5. The figures pertaining to the larger group of 36 subjects can be disregarded at this time. The basal pressure of this group becomes elevated after test 1, the resting pressure rising 5.1 mm. Hg at the systolic level and 3.8 mm. at the diastolic level. This figure recedes toward the initial level in test 3 but in tests 4 and 5 begins to rise again, perhaps owing to fatigue and the discomfort of the procedure.

The maximal systolic pressures obtained after cold immersion show elevations ranging from 23.0 to 30.2 mm. Hg. These elevations are partly due to the contribution of two subjects who had marked pressor responses of 58 and 49 mm. of mercury (average of four tests). The diastolic responses are similar to the systolic except that all pressures are higher in test 5 than in the preceding tests.

The mean rise in arterial pressure following cold immersion shows a marked decrease in pressor response after the first test, especially at the systolic level. The successive mean systolic elevations above the basal level beginning with test 2 are respectively 7.2 mm., 2.4 mm., 4.9 mm. and 2.0 mm. less than the systolic elevation in test 1. The diastolic elevations in tests 2, 3 and 4 are 2.6 mm.; 0 mm. and 0.4 mm. less than the diastolic elevation in test 1, while the diastolic elevation in test 5 is 1.0 mm. greater than that in test 1. The decrease is due, in large part, to the elevation in basal pressure which occurs when the subject is introduced to the painful experience of cold immersion.

TABLE 1.—*Results of Consecutive Cold Pressor Tests in Young Adults: Systolic Pressures*

Test Number	Subjects	Basal		Maximal		Elevation	
		Mean*	S.D.	Mean*	S.D.	Mean*	S.D.
1	10	115.5±2.2	7.0	145.7±3.7	11.7	30.2±2.6	8.3
	36	113.6±1.58	9.5	139.0±2.4	14.5	25.4±1.8	10.7
2	10	120.6±2.8	8.7	143.6±3.3	10.6	23.0±1.6	5.1
	36	115.7±1.9	11.5	136.1±2.4	14.6	20.4±1.4	8.1
3	10	117.9±1.8	5.6	143.7±3.6	11.5	25.8±2.9	9.0
	36	115.8±1.75	10.5	135.8±0.47	2.8	20.0±1.8	10.7
4	10	118.7±2.4	7.5	144.0±3.9	12.3	25.3±2.3	7.4
5	10	119.7±2.67	8.4	147.9±4.1	12.9	28.2±3.1	9.7

* The figure after the ± sign is the standard error of the mean.

TABLE 2.—*Results of Consecutive Cold Pressor Tests in Young Adults: Diastolic Pressures*

Test Number	Subjects	Basal		Maximal		Elevation	
		Mean*	S.D.	Mean*	S.D.	Mean*	S.D.
1	10	57.6±1.8	5.7	75.8±2.5	8.0	18.2±2.6	8.3
	36	59.5±1.3	7.8	76.0±2.7	16.3	16.5±1.4	8.6
2	10	61.4±1.9	6.0	77.0±2.7	8.4	15.6±1.3	4.0
	36	60.7±1.7	10.4	76.5±1.6	9.7	15.9±1.0	5.9
3	10	59.6±0.7	2.3	77.8±2.5	8.0	18.2±1.7	5.4
	36	61.4±1.3	7.6	76.8±2.0	12.2	15.4±1.4	8.2
4	10	60.9±1.5	4.8	78.7±2.7	8.6	17.8±2.0	6.3
5	10	63.1±1.4	4.4	82.3±3.2	10.0	19.2±2.5	8.0

* The figure after the ± sign is the standard error of the mean.

The results of this preliminary study make certain conclusions possible (see below). However, such conclusions rest on several assumptions: (1) The pretest basal pressure is very close to the patient's resting blood pressure. (2) The subject will respond maximally to each immersion stimulus. (3) No other potent vasomotor stimuli are operating during the procedure.

CONCLUSIONS FROM THE PRELIMINARY STUDY

(1) A consistent response is obtained when the cold immersion stimulus is applied repeatedly to the same individual.

(2) There is a noticeable elevation in the basal pressure after the individual has been subjected to the first cold pressor test. This is

TABLE 3.—*Response of Intra-arterial Pressure to a Cold Stimulus in 42 Young Adults*

Pressures, mm. of mercury	Tests	Systolic			Diastolic		
		Mean*	S.D.	Range	Mean*	S.D.	Range
Basal	42	113.4 ± 1.43	9.3	97–138	60.4 ± 1.23	8.0	48–83
	136	115.5 ± 0.86	10.03	90–140	60.9 ± 0.7	8.11	48–84
Maximal	42	137.8 ± 2.16	14.0	121–171	78.9 ± 1.5	9.7	61–99
	136	138.0 ± 1.05	12.25	104–177	77.3 ± 0.88	10.32	60–111
Rise in pressure	42	24.4 ± 1.57	10.2	8–49	18.5 ± 1.23	8.0	4–36
	136	22.6 ± 0.46	5.34	4–58	16.3 ± 0.36	4.19	4–42

* The figure after the ± sign is the standard error of the mean.

less marked at the diastolic level than at the systolic level.

(3) This elevation in the basal pressure after the first cold immersion accounts, in large part at least, for the reduction in pressor response of subsequent tests.

(4) There is no evidence in this data that "cold adaptation," as described by Wolf and Hardy,[15] takes place in the human subject when the time of immersion is limited to 1 minute.

(5) There is probably a limit in each individual to the maintenance of the steady state.

GROUP II: MODIFIED STUDY OF REPEATED TESTS ON 36 YOUNG ADULTS

This group consists of the 10 subjects in the first group and 26 other subjects. There were nine men, aged 20 to 32 years (average 23.7 years) and 27 women, aged 18 to 25 years (average 20.2 years). The findings in these healthy young adults are presented, along with those in group I, in tables 1 and 2. The smaller number of repeated tests (three consecutive tests at 15-minute intervals) in the larger group seems to give a more accurate estimation of the true pressor response in young adults. The diastolic pressor response in test 1 in each group was 18.2 (group I) and 16.5 mm. Hg (group II).

RESULTS OF THE STUDY OF THE ENTIRE GROUP OF HEALTHY YOUNG ADULTS

The response of the intra-arterial pressure of 42 healthy young adults to cold stimulation is presented in table 3. This group was made up of nine men, aged 20 to 32 years (average 23.7 years), and 33 women, aged 18 to 32 years (average 20.6 years).

The data provided by these young adults are presented as single tests in each individual, also as 136 tests in 42 subjects. In clinical medicine the cold immersion stimulus is used as a single test (the cold pressor test) to estimate vascular reactivity. The response of these 42 young adults to single tests is reported because such traetment is directly comparable with clinical results. Multiple tests in this group were examined to accumulate data on the response of healthy subjects to the cold immersion stimulus. The basal pressures obtained from the 42 subjects in the two groups of tests show close resemblance. The mean systolic level in the first tests is 2.1 mm. Hg lower and at the diastolic level 0.5 mm. lower than the values in the multiple tests. The range of blood pressures from which these samples were drawn is quite wide, but only one subject was at the upper limit of the range of the normal population by the standards of Master and associates.[12] This female subject, referred to above, had an indirect blood-pressure determination of 130/90, while the limit of Master and associates for this group is 130/85.

The maximal pressures are shown for the two groups immediately below the basal pressures. The data for 42 and 136 tests show very close correlation. The mean elevation in pressure ("rise") recorded in these subjects after cold immersion varies in a wide range from 4 to 58 mm. Hg at the systolic level and from 4 to 42 mm. at the diastolic level. The mean rise in these individuals, either in single or in multiple tests, is of considerable magnitude, that is, systolic elevations of 24.4 and 22.6 mm. Hg and diastolic increases of 18.5 and 16.3 mm. respectively. The standard error of the mean and the standard deviation of the

TABLE 4.—*Time Required for Maximal and Half-maximal Response to a Cold Stimulus in 42 Young Adults*

	Tests	Systolic			Diastolic		
		Mean*	S.D.	Range	Mean*	S.D.	Range
Time† to maximal pressure	42	55.9 ± 2.44	15.8	4–72	56.4 ± 2.18	14.1	3–71
	136	56.0 ± 1.27	14.7	4–88	54.4 ± 1.09	12.7	3–87
Time† to ½-maximal pressure	42	68.8 ± 2.95	19.1	7–104	66.0 ± 2.38	15.5	6–89
	136	67.4 ± 1.29	14.95	7–104	67.7 ± 1.17	13.6	6–110

* The figure after the ± sign is the standard error of the mean.
† Time in seconds after immersion.

larger group of tests are definitely smaller than those of the 42 tests, suggesting that the larger group is approaching the true mean.

The time, in seconds after immersion, taken to reach the maximal elevation in pressure is shown in the upper half of table 4. The time taken to pass through the maximal elevation and reach a value of one-half maximal pressure is shown in the lower half of the table. This one-half maximal time is measured in seconds from the moment of immersion of the hand in ice water. The results in the two groups of tests are very similar. The range of response times and the significance of these results will be discussed with the graphs of distribution.

MEAN ELEVATION OF ARTERIAL PRESSURE FOLLOWING COLD IMMERSION

The distribution of the elevation of intra-arterial pressure in 136 cold pressor tests on 42 young adults is shown in figure 4. The average pressor responses for the entire 136 tests are indicated by vertical arrows at the top of the graph. Sixty-two per cent of the systolic elevations lie between 15 mm. and 30 mm. Hg, 86 per cent of the group had responses less than 30 mm. and 98 per cent were less than 40 mm. for the diastolic response, 78 per cent of the elevations lie between 10 mm. and 30 mm. Hg, and 98 per cent of the elevations were less than 30 mm. Hg. These data were also plotted as the logarithm of the values for pressure elevation but the contour of the graph did not change significantly. This logarithmic graph is not shown here.

The pressor responses, both systolic and diastolic, group themselves around a major peak at about 13 mm. Hg and a minor peak at the level of 26 mm. Hg. The data of cold pressor responses on many thousands of young

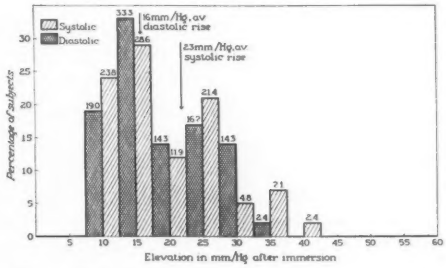


FIG. 4. Percentage distribution of the elevation of systolic and diastolic intra-arterial pressure following cold immersion (mean values from 136 tests in 42 young adults).

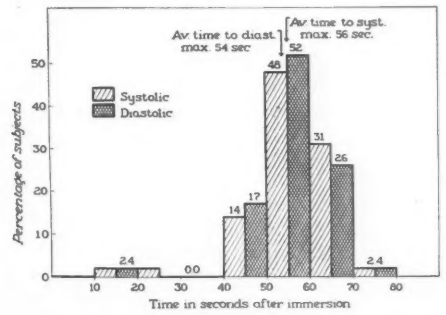


FIG. 5. Percentage distribution of the time required to reach maximal systolic and diastolic pressure after cold immersion (mean values of 136 tests in 42 young adults).

subjects might show that, in respect to the cold pressor test, there are two or more "kinds" of individuals.

TIME FROM IMMERSION TO MAXIMAL ELEVATION OF PRESSURE

The time, in seconds, from immersion to maximal elevation of pressure in 136 cold pressor tests on these 42 young adults is shown in figure 5. The times to maximum, at the

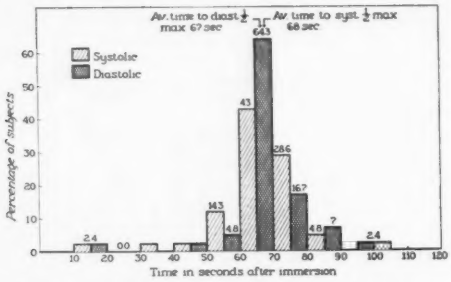


FIG. 6. Percentage distribution of the time required to reach one half the maximal systolic and diastolic pressure after cold immersion (data from 136 tests in 42 young adults).

systolic level, are concentrated so that 80 per cent of the group lie between 50 and 70 seconds after immersion. The entire group had the highest elevation before 80 seconds, that is, within 20 seconds after stimulation was withdrawn. The times to diastolic maximum are almost identically grouped; 79 per cent of the responses, at this level, fall between 50 and 70 seconds after immersion. One hundred per cent of the diastolic rises are completed within 80 seconds of the application of stimulation.

The principal feature of figure 5 is the promptness of the pressor response and the narrow limits of the reaction times in these individuals. The mean response times are shown at the top of the graph by vertical arrows.

TIME FROM IMMERSION TO ONE-HALF MAXIMAL PRESSURE

The time, in seconds, from immersion to the occurrence of one half the maximal pressure in 42 young adults is shown in figure 6. The half-maximal time is a measure of the time required, by the vasomotor system, for recovery from the cold immersion stimulus. The time of return to basal pressure is very difficult to determine with precision because the blood pressure is continually changing. The half-maximal time marks the moment when much of the pressor effect has passed off and the arterial pressure has declined midway to its resting level.

The principal feature in figure 6 is, as in figure 5, the promptness with which the vasomotor system readjusts to the pressor stimulus. The pressor response is a definite but a transient phenomenon. At the systolic level 72 per cent of the group had passed from maximal pressure to half-maximal pressure within 20 seconds, that is, between 60 and 80 seconds. Within the same short period, 81 per cent of the diastolic pressures declined from the greatest elevation midway to the basal level. Within 50 seconds of the cessation of the stimulus, the systolic pressures of the entire group had reached the half-maximal point and 10 seconds earlier, all the diastolic pressures had completed this part of the recovery.

The mean systolic and diastolic half-maximal times are shown by vertical arrows at the top of the graph.

ELECTROCARDIOGRAPHIC CHANGES DURING COLD IMMERSION

Electrocardiographic changes were limited to transient conduction disturbances (sinus arrhythmia) and, in one case, occasional nodal extrasystoles. These changes were associated with distortion of the concurrent pulse wave but did not cause a persistent change in the amplitude of the pressure pulse.

COMPARISON OF THE SIMULTANEOUS DIRECT-INDIRECT BLOOD-PRESSURE MEASUREMENTS

In this study, the direct arterial pressure was recorded from the right radial artery and the indirect arterial pressure was estimated over the right brachial artery. The error introduced by this arrangement can be estimated by examining the comparative values for direct brachial and radial arterial pressures as the percentage of central (arterial) pressure according to Kroeker[16] given in table 5. These are average values from 12 normal subjects, the central pressure being measured in the aorta near the arch or in the left subclavian artery near its origin from the aorta. Therefore,

TABLE 5.—*Direct Brachial and Radial Arterial Pressures as Percentage of Central Arterial Pressure (From Kroeker)*

	Systolic	Diastolic	Mean
Brachial	109	96	98
Radial	112	93	94

TABLE 6.—*Difference Between Simultaneous Direct and Indirect Blood-Pressure Determinations in 35 Young Adults*

Pressure, mm. of mercury	Paired estimations	Systolic			Diastolic		
		Mean*	S.D.	Range	Mean*	S.D.	Range
Basal.....	289	+9.74 ± 0.61	10.4	−18 to 34	−7.28 ± 0.48	8.2	−31 to 20
Maximal.....	62	+16.2 ± 1.3	10.2	−7 to 40	−11.1 ± 1.08	8.6	−25 to 9

* The figure after the ± sign is the standard error of the mean.

for the purpose of the direct-indirect comparison discussed below, direct brachial and radial pressures are almost identical.

Simultaneous direct and indirect blood-pressure determinations were compared in 35 of the 42 young adults taking part in this study.

This comparison was made possible by a compromise between the demands of the two technics. When the recording needle lies in the right radial artery and the blood-pressure cuff is inflated on the right upper arm, both needle and cuff cannot record the arterial pressure at the same time. The period of immersion in ice water was divided in the following manner: the technician, who carried out all the indirect pressure determinations, was instructed to make her estimations in the period between 20 seconds and 50 seconds after immersion. The direct maximal pressure was then identified in the period after the 50-second interval.

The recommendations of the Committee on Standardization of Blood Pressure Readings of the American Heart Association[17] were followed in these indirect pressure determinations. The technician had used the muffling of sounds as the indication of diastolic blood pressure for many years in the peripheral vascular laboratory of this institution. This criterion was used during this project. During the resting or basal period of the direct arterial-pressure recordings 289 paired estimations were made and 62 direct-indirect comparisons were obtained at the maximal elevation of pressure, following cold immersion. Table 6 shows the difference between these simultaneous determinations but gives no direct information about the original pressures which were compared to devise these data.

The reference point in these comparisons is always the direct arterial-pressure estimation, that is, +9.7 means that the direct pressure was 9.7 mm. Hg higher than the simultaneous indirect determination. When the range of pressures from which the mean pressure was derived is quoted, −18 means that the lowest direct estimation was 18 mm. Hg less than its simultaneous indirect estimation, and +34 means that the direct pressure was 34 mm. of mercury greater than the indirect pressure. The first part of table 6 shows that when simultaneous pressure determinations are made with these two methods, the direct systolic pressure will be, on the average, 9.7 mm. Hg higher than the indirect systolic estimation.

At the other level, the direct diastolic pressure will be 7.3 mm. Hg less than the indirect diastolic figure. The direct arterial-pulse pressure is, on the average, 17 mm. of mercury greater than the indirect measure of the systolic-diastolic difference.

The difference between the two methods is definitely increased when the maximal pressures after cold stimulation are compared. Dameshek and Loman[18] found that the indirect error increases as the pulse pressure increases. In a smaller group of paired estimations at the level of maximal pressor response, the direct systolic pressure was, on the average, 16 mm. Hg higher than the indirect result. The direct diastolic estimation was 11 mm. Hg lower than the diastolic pressure recorded with the cuff at the same instant. The comparisons at the moment of maximal pressor response are not absolutely simultaneous: the operator using the cuff was directed to make her measurements between 20 and 50 seconds of the minute after immersion. The direct maximal pressor response was measured after 50 seconds.

A comparison of the difference between direct and indirect blood-pressure determinations in these 35 healthy young adults with the data from a similar simultaneous examination made by Roberts and associates[19] on 30 elderly

TABLE 7.—*Difference Between Simultaneous Direct and Indirect Blood-Pressure Determinations in 30 Elderly Patients and 35 Young Adults*

	Authors	Persons	Paired readings	Systolic			Diastolic		
				Mean*	S.D.	Range	Mean*	S.D.	Range
Brachial	Roberts 1953	30	30	+3.2 ± 2.8	15.4	−28 to 24	−3.1 ± 1.6	9.0	−24 to 12
Radial	This paper	35	289	+9.7 ± 0.61	10.4	−18 to 34	−7.3 ± 0.48	8.2	−31 to 20

* The figure after the ± sign is the standard error of the mean.

male patients in a veterans' hospital is presented in table 7. As far as can be determined, Roberts and associates used the same recording equipment and a technic similar to that used in this project except that they recorded the direct arterial pressure at the brachial artery. The data on the comparison of radial and brachial arterial pressure, given by Kroeker and referred to in table 5, lead us to believe that the brachial recording of Roberts and associates and the present radial recording can be compared without serious error. The upper row of table 7 displays the results of simultaneous blood-pressure determinations in 30 elderly patients. The lower row of figures repeats the results of the comparison made in this present study. The plus and minus values have the same significance in this table as in table 6.

SUMMARY

The response of the intra-arterial pressure to the cold immersion stimulus was studied in 42 healthy young adults, continuous direct (arterial-pressure) recording being used. The difference between direct and indirect methods of measuring blood pressure was studied in 351 simultaneous determinations in 35 of these young adults. The results of this study are as follows:

(1) These subjects responded to a cold stimulus with a prompt, and usually marked, elevation of arterial pressure. The response is described as "prompt" because 94 per cent of the subjects reached maximal systolic elevation between 40 and 70 seconds after immersion and 96 per cent of the group reached maximal diastolic elevation in this 30-second period. The elevation was marked in most cases except for two subjects who had responses of less than 5 mm. Hg. The average systolic elevation was 22.6 mm. and the average diastolic elevation was 16.3 mm. Hg.

(2) These subjects responded in a consistent manner to repeated cold pressor tests carried out at short (15-minute) intervals. When 10 subjects underwent five consecutive tests, there was a borderline significance in the differences between tests 1 and 2 and also between tests 1 and 3, at the systolic level. There was no significant difference in the responses to the five consecutive tests at the diastolic level.

(3) The recovery from the effects of the cold immersion stimulus is rapid, as assessed by measure of the time from application of the stimulus to return of the arterial pressure to the half-maximal pressure.

(4) The differences between simultaneous direct and indirect blood-pressure determinations in 35 young adults were as follows: the direct basal systolic pressure averaged 9.7 mm. Hg higher than the indirect systolic pressure; the direct basal diastolic reading was lower, on the average, by 7.3 mm. Hg. The difference between the two methods was increased when the comparison was made at the moment of maximal pressor response. At this time, the direct systolic pressure was, on the average, 16.2 mm. Hg higher than the indirect systolic pressure. At the diastolic level the direct pressure determination was 11.1 mm. Hg lower than the indirect measure. Thus, the pulse pressure determined directly was 27.3 mm. Hg wider than the indirect pulse pressure.

SUMMARIO IN INTERLINGUA

Le responsa del pression intra-arterial al stimulo de immersion algide esseva studiate in 42 juvene adultos normal. Le methodo usate esseva le continue directe registration del pression arterial. Le elevation systolic media esseva 22,6 mm Hg; le elevation diastoli

n dian esseva 16,3 mm Hg. Le differentias inter l directe e le indirecte methodo de mesurar le p ession sanguinee esseva studiate in 35 del r esme juvene adultos. Esseva executate 351 d terminationes simultanee con le duo metho- d s. Le valor median del pression systolic s cundo le methodo directe esseva 9,7 mm Hg p us alte que secundo le methodo indirecte. L e valor median del pression diastolic secundo l methodo directe esseva 7,3 mm Hg plus i asse que secundo le methodo indirecte.

REFERENCES

1 Hines, E. A., Jr. and Brown, G. E.: A standard stimulus for measuring vasomotor reactions: Its application in the study of hypertension. Proc. Staff. Meet., Mayo Clin. **7:** 332, 1932.

2 Briggs, J. F. and Oerting, H.: Vasomotor response of normal and hypertensive individuals to thermal stimulus (cold). Minnesota Med. **16:** 481, 1933.

3 Feldt, R. H. and Wenstrand, D. E. W.: The cold-pressor test in subjects with normal blood pressure. Am. Heart J. **23:** 766, 1942.

4 Hines, E. A., Jr., and Brown, G. E.: A standard test for measuring the variability of blood pressure: Its significance as an index of the prehypertensive state. Ann. Int. Med. **7:** 209, 1933.

5 Hines, E. A., Jr., and Brown, G. E.: The cold pressor test for measuring the reactibility of the blood pressure: Data concerning 571 normal and hypertensive subjects. Am. Heart J. **11:** 1, 1936.

6 Hines, E. A., Jr.: Reaction of the blood pressure of 400 school children to a standard stimulus. J. A. M. A. **108:** 1249, 1937.

7 Hines, E. A., Jr.: The significance of vascular hyperreaction as measured by the cold-pressor test. Am. Heart J. **19:** 408, 1940.

8 Hines, E. A., Jr.: Vascular Reactivity and Hypertensive Disease. *In,* Hypertension . . . A Symposium, Bell, E. T., ed. Minneapolis, University of Minnesota Press, 1951, p. 331–341.

9 Thacker, E. A.: A comparative study of normal and abnormal blood pressures among university students, including the cold-pressor test. Am. Heart J. **20:** 89, 1940.

10 Dieckmann, W. J., Michel, H. L. and Woodruff, P. W.: The cold pressor test in pregnancy. Am. J. Obst. & Gynec. **36:** 408, 1938.

11 Krieger, V. I. and Weiden, S.: The value of the cold pressor test in the prediction of hypertension and toxaemia in pregnancy. M. J. Australia **1:** 417, 1947.

12 Master, A. M., Garfield, C. I. and Walters, M. B.: Normal blood pressure and hypertension: New definitions. Philadelphia, Lea & Febiger, 1952.

13 Wood, E. H., Lambert, E. and Burchell. H. B.: The application of a strain gauge manometer, a modified ear oximeter and a whole blood cuvette oximeter to the technic of cardiac catheterization. J. Clin. Invest. **28:** 819, 1949.

14 Lambert, E. H. and Wood, E. H.: The use of resistance wire, strain gauge manometer to measure intraarterial pressure. Proc. Soc. Exper. Biol. & Med. **64:** 186, 1947.

15 Wolf, Stewart and Hardy, J. D.: Studies on pain. Observations on pain due to local cooling and on factors involved in the "cold pressor" test. J. Clin. Invest. **20:** 521, 1941.

16 Kroeker, E. J.: A comparison of simultaneous central and peripheral pressure pulses in man. Unpublished data.

17 Bordley, J., III, Connor, C. A R., Hamilton, W. F., Kerr, W. J. and Wiggers, C. J.: Recommendations for human blood pressure determinations by sphygmomanometers. Circulation **4:** 503, 1951.

18 Dameshek, W. and Loman, J.: Direct intra-arterial blood-pressure readings in man. Am. J. Physiol. **101:** 140, 1932.

19 Roberts, L. N., Smiley, J. R. and Manning, G. W.: A comparison of direct and indirect blood-pressure determinations. Circulation **8:** 232, 1953.

Reactivity to Pressor Agents in Hypertension

By Austin E. Doyle, M.D., M.R.C.P. and Harold Black, M.B.(N.Z.), M.R.A.C.P.

The pressor responses to intravenous injections of angiotonin and s-methyl *iso*-thiourea have been studied in 50 hypertensive subjects and 20 normotensive controls. The rises of blood pressure in the two groups were similar, being but slightly greater in the hypertensives. After the blood pressure has been reduced with hexamethonium, however, the pressor responses to angiotonin, s-methyl *iso*-thiourea and noradrenaline are much greater in hypertensives than normotensive subjects. The responses under these conditions to all three pressor agents run parallel to each other, suggesting that there is no specific increase in reactivity in hypertensive subjects, either to angiotonin or noradrenaline. It has been concluded that there is evidence of increased reactivity to pressor substances in hypertensive subjects but that this is not demonstrable until the blood pressure control mechanisms have been inactivated by hexamethonium.

IT IS generally agreed that in human hypertension the blood pressure rise is due to an abnormally high peripheral resistance, the result of constriction of the arterioles While some workers believe that the arteriolar constriction is predominantly due to an overaction of the sympathetic nervous system, others hold the view that it is the result of the presence of a circulatory pressor substance.

The demonstration by Goldblatt[1] that experimental renal ischemia leads to hypertension was followed by the isolation of a pressor substance which was named angiotonin by Page and Helmer[2] and hypertensin by Braun-Menendez and associates.[3] Angiotonin produces vascular constriction by a direct action on the muscle of blood vessels,[4] and would seem to be a substance capable of producing a rise of blood pressure like that which occurs in human hypertension.

Direct evidence that angiotonin is responsible for some of the blood pressure rise in hypertension depends on the demonstration that the substance is present in the blood of hypertensive subjects. Kahn and his co-workers[5] have reported that the concentrations of angiotonin in the blood of patients with malignant hypertension are approximately 20 times as great as in the blood of normal control subjects. The same workers found that in non-malignant essential hypertension the angiotonin concentration, although slightly greater than in the controls, was too small to allow conclusions to be drawn as to its effectiveness in producing the vasoconstriction in these patients.

The further possibility remains, however, that hypertensive subjects might react more vigorously than normals to this substance. If this were so, a normal or slightly raised amount of circulating angiotonin might produce a larger rise of blood pressure in the hypertensive than in the normotensive subject. The action of angiotonin in normotensive man has been described by Bradley and Parker[6] and Wilkins and Duncan[7] but except for the report of Gregory and his colleagues,[8] who studied the effects of angiotonin in hypertensive subjects after spinal anesthesia, we have found no reference to its administration to hypertensive patients.

The possibility, moreover, that the blood vessels of hypertensive subjects are unusually sensitive to many pressor stimuli has been extensively studied in man and in animals, using both chemical and nervous stimulation. In man, the cold pressor test was found by Hines and Brown[9] to produce larger responses in hypertensive subjects and in subjects susceptible to hypertension, than in normotensive subjects. Reports of other workers, however, have conflicted with these findings. Alam and Smirk[10] found that while large pressor responses to cold and to the reflex from voluntary muscle were more common in cases of essential hypertension than in normal subjects, yet in many cases of hypertension the response was no

From the Department of Medicine, Otago University Medical School, Dunedin, New Zealand.

greater than in some normal subjects. Russek and Zohman[11] reported similar results with the cold pressor test, but Pickering and Kissin[12] could find no difference in the responses to cold in the hypertensive and normotensive groups.

The responses to chemical stimuli have also been extensively examined. Clough[13] found that in hypertensive subjects the rises of blood pressure produced by adrenaline were much greater than those in normal subjects. Lian, Stoicesco and Vidrasco[14] found that the vascular reactions produced by adrenaline, and other stimuli, were greater in hypertensives than in normals. Goldenberg and his coworkers[15] reported that hypertensive patients had similarly exaggerated pressor responses to noradrenaline, whilst Raab[16] has reported that a much greater rise in blood pressure occurs in hypertensive subjects than in normals after the inhalation of carbon dioxide. In contrast to these findings, however, many workers have reported similar pressor responses in hypertensive and normotensive subjects. Fatheree and Hines[17] noted no distinct difference in the response of hypertensive and normotensive subjects to adrenaline and similar results were reported by Gordon and Levitt[18] and by Judson and associates.[19, 20] Page [21] has reported that angiotonin produces similar rises of blood pressure in renal hypertensive dogs and in normal dogs.

It seems that the evidence concerning the pressor reactivity in hypertensive and normotensive subjects is conflicting; while some have found exaggerated pressor responses in hypertensives, many others have found similar responses in the two groups. This may be due to the fact that investigation of this problem is complicated by the fact that the different starting levels of the blood pressure may themselves determine differences in the degree to which hypertensives and normotensives respond to various stimuli. In addition, the extent to which the homeostatic regulatory mechanisms oppose rises of pressure from pressor stimuli may not have precisely the same effects in hypertensives as they have in normotensives.

We report here a comparison of the pressor effects of angiotonin in hypertensive and normotensive subjects. A comparison of the pressor effects of angiotonin and the effects of noradrenaline and the synthetic pressor agent s-methyl *iso*-thiourea has also been made in the two groups. The observations have been made under standard conditions, and also after ganglionic blockade with hexamethonium. The preliminary administration of hexamethonium has the advantage that it not only renders the starting levels of the blood pressure more nearly comparable, but it also minimises interference from the homeostatic blood pressure control mechanisms. Some observations have also been made after the blood pressure had been reduced by veratrum alkaloids.

Methods

Blood pressures were recorded by the auscultatory method, in accordance with the recommendations of the Committee for the Standardization of Blood Pressure Readings of the American Heart Association and the British Cardiac Society (1939).

The subjects were recumbent in a quiet room. The blood pressure was measured every 30 seconds by one of us. After a preliminary period of about 10 minutes, a needle was introduced into the median basilic vein in the other arm, and a slow infusion of 5 per cent glucose was commenced. After this, injections were made through a three-way tap. These were given without the patient's knowledge of the nature of the injection. Occasional dummy injections of 5 per cent glucose were given to exclude pressor responses other than those attributable to the pressor agent being studied.

In the experiments in which hexamethonium was used 20 mg. of hexamethonium was injected every three minutes, until two successive doses produced no further fall in blood pressure. When the veratrum alkaloids were used 0.5 mg. of Veriloid (Riker) was given at two-minute intervals until premonitory toxic symptoms were reported, or until the blood pressure had reached a near normal level.

The doses used were: angiotonin 5 units, noradrenaline 2 μg. and s-methyl *iso*-thiourea 50 mg.

Selection of patients: The hypertensive subjects were selected from those attending the hypertensive clinic. All had casual blood pressures consistently higher than 180/100 mm. Hg. A normotensive group of similar age was selected from surgical patients awaiting operation, or from healthy normotensive volunteers. In this group the casual blood pressures were consistently below 150/90 mm. Hg.

Results

(1) *Effects of Angiotonin in Hypertensive and Normotensive subjects*

The rises of blood pressure produced by angiotonin were examined in 50 hypertensive subjects and in 20 normotensive controls (fig. 1). Repeated injections of the same dose to individual patients on the same day and on different days produced similar rises of blood pressure. The average rise of blood pressure in the hypertensive group was 26/20 mm. Hg; the average rise in the control group was 20/16 mm. Hg.

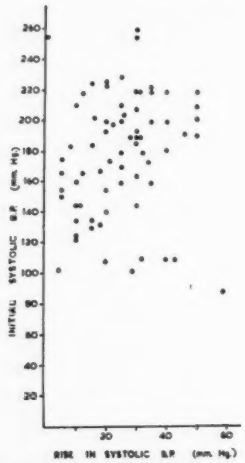


FIG. 1. The rise in systolic blood pressure in response to the intravenous injection of 5 units of angiotonin in 50 hypertensive subjects (solid circles) and 20 normotensive subjects (open circles).

The duration of the pressor effect was substantially the same in the two groups, the average duration being five minutes in each group.

In agreement with the findings of most other workers, the pulse slowed in most of the normotensive group, the slowing on occasion being pronounced. There was, however, no striking alteration in the pulse rate in the hypertensive group.

Most of the hypertensive subjects had essential hypertension. Four had hypertension associated with manifest renal disease, 8 had hypertension which was thought to have followed a pre-eclamptic toxemia of pregnancy and one had coarctation of the aorta. No striking differences were noted either in the size of the blood pressure rise or in the duration of the response in these various groups of patients.

(2) *Effects of S-Methyl Iso-Thiourea in Normotensive and Hypertensive Subjects*

Ten of the subjects who had been tested with angiotonin were subsequently given injections of s-methyl *iso*-thiourea. Of the subjects examined, five were hypertensive and five normotensive. The subjects were selected because they had shown extreme variation in the pressor response to angiotonin. Although the effects of 50 mg. of s-methyl *iso*-thiourea were usually greater than the effects of 5 units of angiotonin, the responses of the individual patients to the two drugs were otherwise similar, in the sense that those who exhibited large rises of blood pressure with one substance also had large rises of blood pressure with the other, whilst those in whom the pressor effects of one were slight similarly showed smaller responses to the other drug.

(3) *Effects of Angiotonin in Hypertensive and Normotensive Subjects after Ganglionic Block with Hexamethonium*

Seventeen hypertensive subjects and 17 normotensive subjects were tested with angiotonin after the blood pressure had been reduced by large intravenous doses of hexamethonium. Repeated doses of hexamethonium were given, and when an apparently stable level of blood pressure had been reached, the angiotonin was injected. The results are shown in figure 2. The pressor response was now much greater in the hypertensive group than in the normotensive group. The average rise of blood pressure in the hypertensive subjects was 45/32 mm. Hg as compared with 22/18 mm. Hg for the control group under the same conditions. The responses in the hypertensive group were almost doubled by ganglionic block, whereas in the control group the augmentation of the pressor response produced by hexamethonium was usually much smaller. The extent to which the blood pressure of the hypertensive subjects fell after hexamethonium did

ot seem to be an important factor in determining the degree to which the pressor response was augmented, for both those with large falls of blood pressure with hexamethonium and those with small falls had similarly augmented pressor responses. There was less individual variation in the response to angiotonin after ganglionic block than under control conditions, but some variation in the response was still found.

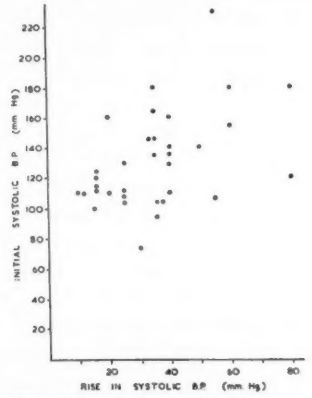


FIG. 2. The rise in systolic blood pressure in response to the intravenous injection of 5 units of angiotonin in 17 hypertensive subjects (solid circles) and 17 normotensive subjects (open circles) after ganglionic blockade with hexamethonium. For detail see text.

(4) *Comparison of the Effects of Angiotonin, Noradrenaline and S-Methyl Iso-Thiourea after Ganglionic Block*

The pressor responses to angiotonin, noradrenaline and the synthetic pressor agent, s-methyl *iso*-thiourea, were compared in 20 subjects, 13 hypertensive and 7 normotensive, after hexamethonium had been given. The subjects were selected because of the wide variation in their previous responses to angiotonin under similar conditions. The results are shown in figures 3 and 4. It is clear that the sensitivity to the three substances runs parallel, for those with large responses to angiotonin also had large responses to the other substances tested. It is also clear that the pressor responses to all three substances are consistently greater in the hypertensive group than in the normotensive.

(5) *Effect of Angiotonin after Administration of Veratrum in Hypertensive Subjects*

In 10 hypertensive subjects, the blood pressure was reduced to near normal levels by the intravenous administration of Veriloid, an

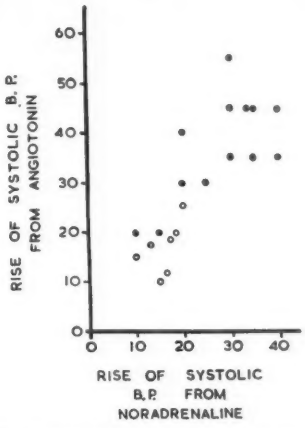


FIG. 3. Comparison of the pressor responses to 5 units of angiotonin and 2 μg. of noradrenaline in 13 hypertensive subjects (solid circles) and 7 normotensive subjects (open circles) after ganglionic blockade with hexamethonium.

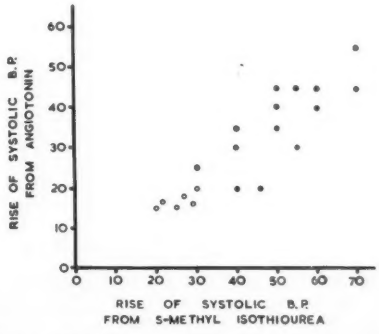


FIG. 4. Comparison of the pressor responses to 5 units of angiotonin and 50 mg. of s-methyl *iso*-thiourea in 13 hypertensive subjects (solid circles) and 7 normotensive subjects (open circles) after ganglionic blockade with hexamethonium.

alkaloidal extract of veratrum viride. After the blood pressure had been so reduced, the pressor response to angiotonin was studied. The responses were similar to those obtained after hexamethonium, the average response being 51/31 mm. Hg. The pressor responses

were greater in all the patients after the blood pressure had been lowered than they were under resting conditions.

Discussion

The three pressor agents which have been studied in this work have similar sites of action but are otherwise widely dissimilar. Two of them, angiotonin and noradrenaline, although unrelated chemically are both substances which occur naturally, but s-methyl *iso*-thiourea is a synthetic substance. The cardiac output in man is reduced by angiotonin,[22] and by noradrenaline[15] and it seems likely that it is not raised by s-methyl *iso*-thiourea. All three drugs produce rises of blood pressure primarily by a direct action on the blood vessels.

It cannot be assumed, however, that the rises of blood pressure which follow the administration of any pressor substance under ordinary test conditions give any precise indication of the degree of vascular constriction which the substance has caused; for there is evidence that rises or falls of blood pressure produced in a variety of ways may be buffered by regulatory mechanisms, which tend to maintain the blood pressure at a constant level.[23, 24] It seems probable that the rise of blood pressure which follows the administration of a pressor substance represents the resultant of the vascular constriction produced by the pressor stimulus and the modification of this produced by reflex homeostatic regulatory mechanisms.

The rises in blood pressure produced by the intravenous administration of angiotonin and s-methyl *iso*-thiourea are usually a little larger in hypertensives than in normotensives. But, following ganglionic blockade with large doses of hexamethonium, the rises of blood pressure in the hypertensives are considerably larger than in the normotensives. The extensive degree of blockade by hexamethonium which occurs with intravenous doses of the order of 1 to 2 mg. per kilogram, such as we used, undoubtedly severely limits and may even abolish the capacity of the reflex homeostatic regulatory mechanisms to counter changes in blood pressure. The profound postural hypotension which occurs with the doses we have used suggests that this is so. The average pressor responses to angiotonin and to s-methyl *iso*-thiourea under these conditions are about twice as large in hypertensives as in normotensive subjects.

A possible interpretation of this result is that pressor reactivity is greater in hypertension than in normotension and that, when this is not manifest under ordinary circumstances, it is because the activity of the regulatory mechanisms limits the rises of blood pressure to a greater extent in the hypertensive than in the normotensive.

An alternative explanation is that the rises of blood pressure produced by pressor agents are greater from the lower levels of blood pressure which result from methonium administration. We have insufficient evidence to comment on this possibility.

The changes in the responses of the blood pressure to various pressor agents may involve adjustments throughout the cardiovascular system. Certainly, on the evidence presented, it cannot be assumed that such changes are confined to alterations in the state of contraction of blood vessels. Some of our observations, however, seem to warrant further discussion.

In the absence of ganglionic blockage, the magnitudes of the blood pressure rises, in response to a standard dose of angiotonin, vary from one person to another. This statement applies both to normotensives and to hypertensives. The differences in the pressor responses are considerable. A less reactive person may have a rise of 5/0 mm. Hg from 5 units of angiotonin, whereas a more reactive person may have a rise of 50/30 mm. Hg. These variations, however, are not fortuitous because when angiotonin is compared with the synthetic substance s-methyl *iso*-thiourea and with noradrenaline, it is found that the patients who give big rises with angiotonin also give big rises with noradrenaline and s-methyl *iso*-thiourea; likewise, small responses to angiotonin are associated with small responses to noradrenaline and s-methyl *iso*-thiourea. Therefore, we may conclude that large and small responses to angiotonin reflect changes in the

reactivity to pressor agents in general, rather than a specific sensitivity to angiotonin.

A further conclusion may be drawn, namely, that if circulating pressor agents play a part in maintaining the blood pressure level in hypertension or in normotension, then the extent to which they influence the blood pressure level depends to an important degree upon the patient's responsiveness to the pressor agent. Amounts of angiotonin or of certain other pressor agents which cause substantial blood pressure increases in reactive patients, have very little action in unreactive patients. Hence, the presence or absence of hypertension could depend as much upon the reactivity of the patient to a stimulus as on the magnitude of the stimulus.

The fact that increased pressor activity can be demonstrated, not only in essential hypertension but also in renal hypertension, and post-toxemic hypertension, is favorable to the conclusion that the increased reactivity may be a result of continued blood pressure elevation and possibly due to cardiovascular hypertrophy.

If increase of cardiovascular reactivity is an effect of continued hypertension, then the development of abnormal sensitivity to pressor stimuli is probably one of the mechanisms which lead to the perpetuation of the hypertensive state, irrespective of the initiating cause.[25]

Summary and Conclusions

Under standard conditions, hypertensives have slightly greater pressor responses to angiotonin and to s-methyl *iso*-thiourea.

After ganglionic blockade with hexamethonium, these substances and also noradrenaline induce much larger pressor responses in hypertensives than in normotensives.

The increased pressor response following ganglionic blockade is present in essential, renal and post-toxemic hypertension.

Some patients react strongly to all three substances, and other patients give but small rises of blood pressure. In almost all instances high or low reactivity to angiotonin is associated with reactivity of corresponding magnitude to the administration of the other pressor substances.

There seems to be good evidence that there are variations in the *reactivity of the circulatory system as a whole* to pressor stimuli; this variation from one person to another is likely to be an important factor in determining the effect of any humoral pressor agents on the blood pressure level.

Acknowledgment

We are indebted to Professor F. H. Smirk for much helpful advice and criticism. The angiotonin was supplied through the courtesy of Dr. Oscar Helmer of the Eli Lilly Company. This work was supported by the Life Insurance Medical Research Fund of Australia and New Zealand.

Summario in Interlingua

Le responsas pressorial a injectiones intravenose de angiotonina e s-methylo-*iso*-thiourea esseva studiate in 50 individuos hypertensive e 20 individuos normotensive de controlo. Le augmento del pression sanguinee esseva simile in le duo gruppos; in le individuos hypertensive illo esseva levemente plus grande. Del altere latere, si le pression sanguinee esseva primo reducite per medio de hexamethonium, le responsas pressorial a angiotonina, s-methylo-*iso*-thiourea, e noradrenalina, le responsas pressorial esseva multo plus grande in le gruppo hypertensive que in le gruppo normotensive. Sub iste conditiones le responsas al tres mentionate agentes se manifesta in formas parallel. Isto pare significar que individuos hypertensive non es characterisate per un augmento specific de reactivitate a angiotonina o a noradrenalina. Le conclusion a derivar ab iste constatationes es que in individuos hypertensive il ha un augmentate reactivitate a substantias pressorial sed que iste augmento non es demonstrabile usque le mechanismos regulatori del pression sanguinee es inactivate per hexamethonium.

REFERENCES

[1] Goldblatt, H.: Studies on experimental hypertension. V. The pathogenesis of experimental hypertension due to renal ischemia. Ann. Int. Med. **11:** 69, 1937.

[2] Page, I. H. and Helmer, O. M.: A crystalline pressor substance (angiotonin) resulting from

the reaction between renin and renin-activator. J. Exper. Med. **71:** 29, 1940.

[3] Braun-Menendez, E., Fasciolo, J. C., Leloir, L. F. and Muñoz, J. M.: The substance causing renal hypertension. J. Physiol. **98:** 283, 1940.

[4] Corcoran, A. C. and Page, I. H.: The effects of angiotonin on renal blood flow and glomerular filtration. Am. J. Physiol. **130:** 335, 1940.

[5] Kahn, J. R., Skeggs, L. T., Jr., Shumway, N. P. and Wisenbaugh, P. E.: The assay of hypertensin from the arterial blood of normotensive and hypertensive human beings. J. Exper. Med. **95:** 523, 1952.

[6] Bradley, S. E. and Parker, B.: Hemodynamic effects of angiotonin in normal man. J. Clin. Invest. **20:** 715, 1941.

[7] Wilkins, R. W. and Duncan, C. N.: The nature of the arterial hypertension produced in normal subjects by the administration of angiotonin. J. Clin. Invest. **20:** 721, 1941.

[8] Gregory, R., Levine, H. and Lindley, E. L.: The site of action of angiotonin; the pressor effects of angiotonin on patients having essential hypertension and possible relationships to the pathogenesis of essential hypertension. Texas Rep. Biol. & Med. **2:** 121, 1944.

[9] Hines, E. A. and Brown, G. E.: A standard test for measuring the variability of blood pressure: its significance as an index of the prehypertensive state. Ann. Int. Med. **7:** 209, 1933.

[10] Pickering, G. W. and Kissin, M.: The effects of adrenaline and of cold on the blood pressure in human hypertension. Clin. Sc. **2:** 201, 1936.

[11] Russek, H. I. and Zohman, B. L.: Influence of age upon blood pressure response to the cold-pressor test. Am. Heart J. **29:** 113, 1945.

[12] Alam, G. M. and Smirk, F. H.: Blood pressure raising reflexes in health, essential hypertension, and renal hypertension. Clin. Sc. **3:** 259, 1938.

[13] Clough, P. W.: A study of the cardiovascular reaction to epinephrin. Epinephrin sensitiveness in patients with hypertension. Bull. Johns Hopkins Hosp. **31:** 266, 1920.

[14] Lian, C., Stoicesco, S. and Vidrasco, C.: De l'etat du système nerveux végétatif dans l'hypotension et l'hypertension arterielles permantes. Presse méd. **37:** 1309, 1929.

[15] Goldenberg, M., Pines, K. L., Baldwin, E. de F., Greene, D. G. and Roh, C. E.: The hemodynamic response of man to nor-epinephrine and epinephrine and its relation to the problem of hypertension. Am. J. Med. **5:** 792, 1948.

[16] Raab, W.: Central vasomotor irritability. Contribution to the problem of essential hypertension. Arch. Int. Med. **47:** 727, 1931.

[17] Fatherree, T. J. and Hines, E. A.: The blood pressure response to epinephrine administered intravenously to subjects with normal blood pressure and to patients with essential hypertension. Am. Heart J. **16:** 66, 1938.

[18] Gordon, W., and Levitt, G.: Blood pressure changes in normals and in hypertensives after intravenous epinephrine and histamine. J. Clin. Invest. **14:** 367, 1935.

[19] Judson, W. E., Culbertson, J. W., Tinsley, C. M., Litter, J. and Wilkins, R. W.: The comparative effects of small intravenous doses of epinephrine upon arterial pressure and pulse rate in normotensive subjects and in hypertensive patients before and after thoracolumbar sympathectomy. J. Clin. Invest. **29:** 1405, 1950.

[20] Judson, W. E., Epstein, F. H. and Wilkins, R. W.: The comparative effects of small intravenous doses of l-norepinephrine upon arterial pressure and pulse rate in normotensive subjects and in hypertensive patients before and after thoracolumbar sympathectomy. J. Clin. Invest. **29:** 1414, 1950.

[21] Page, I. H.: The pressor response of normal and hypertensive dogs to renin and angiotonin. Am. J. Physiol. **134:** 789, 1942.

[22] Taylor, R. D. and Page, I. H.: The effect of antipressor kidney extract, angiotonin, methyl guanidine and tyramine on cardiac output as measured by the ballistocardiograph in hypertensive and normal persons. Am. J. M. Sc. **205:** 66, 1943.

[23] Barcroft, H., Gaskell, P., Shepherd, J. T. and Whelan, R. F.: The effect of noradrenaline infusions on the blood flow through the human forearm. J. Physiol. **123:** 443, 1954.

[24] Smirk, F. H. and Doyle, A. E.: Unpublished observations.

[25] —: Pathogenesis of essential hypertension Brit. M. J. **1:** 791, 1949.

Mitral Commissurotomy Performed During Anticoagulant Prophylaxis with Dicumarol

By OLE STORM, M.D. AND ANDERS TYBJÆRG HANSEN, M.D.

Since it is possible to perform major surgical interventions on patients with lowered prothrombin-proconvertin concentration we have selected a group of patients suffering from mitral stenosis for further evaluation of this prophylactic measure. These patients are highly predisposed to thromboembolic complications. The controllable risk of hemorrhage might, therefore, be preferred to the heavy risk of thrombosis. The results of our investigations indicate a decrease in incidents of thromboembolism. No serious risk of bleeding is apparently introduced when an accurate and sensitive method of estimating the prothrombin level is used in the control of the treatment.

PATIENTS suffering from mitral stenosis are highly predisposed to thromboembolic accidents. The major risk and most frequent cause of death during and after mitral commissurotomy is cerebral embolism. During surgery, large amounts of tissue thromboplastin enter the blood stream and in this way accelerate the intravascular coagulation. Anticoagulant prophylaxis with Dicumarol will therefore be complete only when instituted before and maintained during and after the operation.

It was shown previously that major surgical operations can be performed under effective anticoagulant prophylaxis with Dicumarol.[1] The operations were successfully accomplished with this treatment at a prothrombin level in the therapeutic range, without increased bleeding or other complications.

Mitral commissurotomy can also be performed safely under effective anticoagulant therapy with Dicumarol.[2] It is the object of this paper to present and discuss the results of one year's treatment.

From the Rigshospitalet, Medical Department B (Head: Prof. E. Warburg, M.D.), Surgical Department D (Head: Prof. E. Husfeldt, M.D.), Surgical Department R (Head: Prof. F. Therkelsen, M.D.), University Hospital of Copenhagen and the Biological Institute of the Carlsberg Foundation (Head: Dr. A Fischer), Copenhagen, Denmark.

This investigation was supported by a grant from the P. Carl Petersen Found, Copenhagen. It is part of the investigations on blood coagulation for which Dr. Tage Astrup of the Biological Institute of the Carlsberg Foundation receives support from the Josiah Macy Jr. Foundation, New York.

METHOD

The level of prothrombin-proconvertin in blood was followed by an accurate one-stage assay (Owren's method[3, 4]). Daily determination of the prothrombin-proconvertin level was considered necessary, especially during the first several days after operation. In agreement with most authors we find the therapeutic level of prothrombin-proconvertin to be between 10 and 30 per cent. Below 5 per cent there is an increased risk of major hemorrhage, but above 10 per cent the risk is insignificant. It is essential that the determination of the prothrombin-proconvertin level be as accurate as possible. Owren's method is very sensitive and reliable and was therefore chosen for our purpose.

Dosage: Four hundred to 500 mg. of Dicumarol were given during the first two days of treatment. The subsequent dosage was determined by the response. Individual variations often occur.[5] Low prothrombin levels on the day of operation were corrected by the use of vitamin K_1 (20 to 50 mg. vitamin K_1, Geigy).[6] Dicumarol was usually given 1 to 2 weeks preoperatively and 3 weeks postoperatively until the patient was effectively ambulatory.

Patients: The patients for Dicumarol prophylaxis were selected in the following way: Patients born on even dates received the treatment, while patients born on uneven dates received no anticoagulant prophylaxis and served as controls. However, some patients born on uneven dates and already under anticoagulant therapy were admitted to the surgical ward. This therapy had been instituted because of recent thromboembolic complication in addition to the valvular disease. We deemed the risk of new thromboembolic incidents too high if the Dicumarol therapy was discontinued, hence the prophylaxis was maintained. From Jan. 15, 1954 to Jan. 15, 1955, 26 patients

with mitral stenosis had a commissurotomy performed under Dicumarol prophylaxis. The untreated control group of patients from the same period also consisted of 26 patients.

Results

Dicumarol Prophylaxis

On the day of operation the prothrombin per cent averaged 20; in 15 cases it was between 10 and 19 per cent, in 10 cases between 20 and 30 per cent and in one case 36 per cent. There was a slight fall in the prothrombin level in the first two or three days after the commissurotomy in 17 cases and a slight increase in four cases. A rather pronounced increase in the prothrombin level was found in five patients who received vitamin K_1 or menadion preoperatively in order to correct a too low prothrombin level. In all cases, the decrease in the prothrombin per cent was followed by a marked increase from the fifth to the seventh day and at the same time there was an increase in the maintenance dose of Dicumarol. In most cases, the daily dose of Dicumarol was 20 to 40 mg. higher in the weeks after the operation than before. In most cases, the prophylaxis was continued three weeks or more after the commissurotomy. Some of the patients were still under anticoagulant treatment when discharged from the hospital and continued this therapy as out-patients. On the whole, the treatment was stopped when the patient was as effectively mobile as before the operation. In two cases, however, the treatment was discontinued shortly after the operation. One of these patients developed severe icterus (possibly due to preoperative blood transfusions: hemolytic icterus); in the other case the treatment was stopped by mistake six days after the operation. A typical curve of the prothrombin-pro-convertin level during the period of treatment and the daily doses of dicumarol is shown in figure 1.

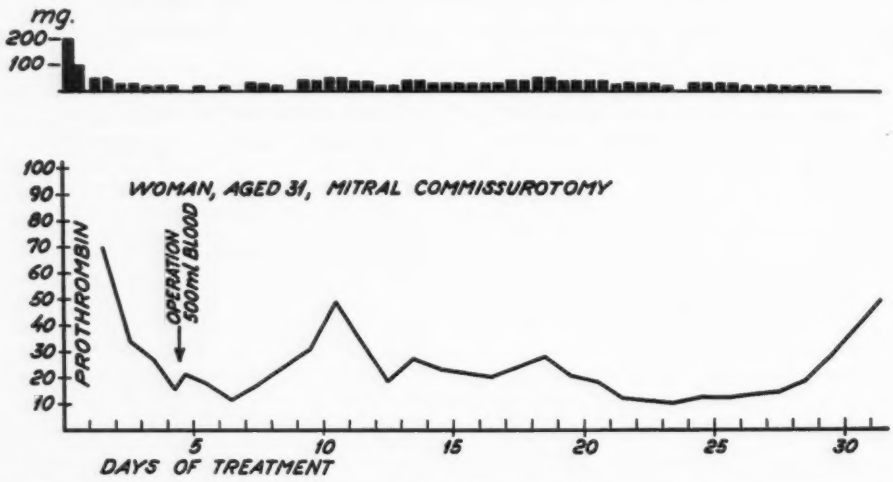


Fig. 1. Mitral commissurotomy. The dosage of Dicumarol (above) and the proconvertin-prothrombin level (in per cent) in blood (below) before, during and after operation.

Hemorrhage

The bleeding during the operations was not measured routinely, but the postoperative loss of blood through drainage and thoracocentesis was measured. This was compared with the loss of blood in the control group and with 50 other cases of mitral valvulotomy performed in the previous year (table 1). The loss of blood in the treated group was on an average 624 ml., in the control group, 813 ml. (In the control group there were a few difficult and complicated operations).

The average amount of blood transfused has also been compared in the two groups. The patients treated with Dicumarol received an

average of 777 ml. blood during the operation and on the days that followed. In the control group, the average amount of blood transfused was 1058 ml. (table 2). (The authors did not administer the transfusions).

These figures show clearly that the postoperative blood loss and the need of blood has not been higher for the patients under anticoagulant prophylaxis than for the patients without this therapy.

Thromboembolic Complications

Ten patients in the Dicumarol-treated group and 13 in the control group were above the age of 40 years. According to most reports, the risk of thromboembolic complications during surgery increases after the age of 40, so there was probably a greater risk of such complications in the control group than in the treated group.

Atrial fibrillation also predisposes to thromboembolism. Seven of the control patients and 11 of the treated patients suffered from atrial fibrillation as a complication of rheumatic heart disease. Postoperative thromboembolic incidents occurred in three of these control patients with fibrillation, while none of the 11 patients under Dicumarol prophylaxis showed signs of these complications. One of the control patients, who developed atrial fibrillation postoperatively, had a cerebral embolus. Among the patients in the treated group who developed postoperative fibrillation, no such complications occurred. In one of the patients under Dicumarol prophylaxis, a fresh atrial thrombus was found upon operating. This patient had only been treated six days preoperatively with Dicumarol, and there were no embolic complications of the commissurotomy, although she suffered from pre- and postoperative atrial fibrillation. One patient in the treated group and one in the control group had old thrombi in the atrium and an extra-auricular valvulotomy was performed.[7] Both survived the operation without complications.

Of the 26 patients in the treated group, 7 patients had had thromboembolic incidents before surgery. No postoperative thromboembolic complications occurred among these or the other Dicumarol-treated patients in the postoperative period (3 to 4 weeks).

In the control group, four patients had had thromboembolic attacks before surgery; two of these patients developed lung infarction postoperatively.

The number of control patients with postoperative thrombotic incidents confirmed clinically was six: one died of cerebral embolism, another still has paralysis of the right arm due to cerebral embolism. Two patients recovered from cerebral embolism and two from pulmonary infarction. In addition, two other control patients suffered from probable post-

TABLE 1.—*Postoperative Hemorrhage after Mitral Commissurotomy*

Patients	Average hemorrhage	Range	Distribution
50 controls before Jan. 15th, 1954.	749 ml.	80–2160	10 below 480 ml. 10 above 1000 ml.
26 controls between Jan. 1954 and Jan. 1955.	813 ml.	125–2125	5 below 510 ml. 5 above 1060 ml.
26 treated between Jan. 1954 and Jan. 1955.	624 ml.	210–1650	5 below 480 ml. 5 above 740 ml.

TABLE 2.—*Amount of Blood Transfused During and After Surgery*

Patients	Average amount of blood transfused	Distribution
50 controls before Jan., 1954.	835 ml.	10 above 1500 ml. 14 between 1000–1500 ml. 25 between 500–1000 ml. 1 nothing.
26 controls between Jan. 1954 and Jan. 1955	1058 ml.	5 above 1500 ml. 17 between 1000–1500 ml. 4 between 500–1000 ml.
26 treated between Jan. 1954 and Jan. 1955.	777 ml.	2 above 1500 ml. 10 between 1000–1500 ml. 14 between 500–1000 ml.

operative embolism: one from a lung infarction and the other from a cerebral embolus.

Discussion

It is well-known that thromboembolic incidents are frequent complications of rheumatic heart disease. Recently, Bigelow[8] reported 39 systemic embolic episodes in 171 patients with mitral stenosis. Seven of these patients (18 per cent) died within one month after the episode, and the rest died within three and one half years. In a survey of 393 embolic episodes in 194 patients with rheumatic heart diseases, Bland[9] found the following features: Single embolic episodes occurred in 79 patients with a mortality of 30 per cent, multiple episodes occurred in 115 patients of whom 55 succumbed.

However, long-term anticoagulant therapy with Dicumarol has been shown to reduce thromboembolism in patients with mitral stenosis, atrial fibrillation and congestive heart failure.[10, 11, 12, 13]

Cerebral embolism is the most frequent cause of death after mitral commissurotomy. This was stated by Bailey[14] who found 12 cases (5 per cent) of cerebral embolism in 235 patients operated on for mitral stenosis. Eight of these 12 patients died. In Bigelow's report,[8] mitral commissurotomy was performed in 88 patients. The total number of thromboembolic episodes was 17 (20 per cent of the cases) and six showed postoperative cerebral embolism (one died). In 150 patients followed-up, the total number of fatal cerebral embolism was six (4 per cent of the patients). The figures of Warren[15] are also striking: 15 (16 per cent) out of 92 patients with mitral stenosis developed embolic episodes postoperatively after commissurotomy. The incidence was higher in a group of patients who previously had had embolic episodes and also in patients with atrial fibrillation. Baden[16] analyzed 106 cases of mitral stenosis operated on at the University Hospital of Copenhagen. Postoperative thromboembolic complications occurred in 20 per cent. Twelve patients died after the operation and in eight of these cases, death was caused by cerebral embolism a few days after the operation.

Anticoagulant prophylaxis with Dicumarol has been used successfully after surgical operations and has reduced the frequency of thromboembolic complications.[17, 18] Usually this therapy has been initiated after the operation, but in some instances the first dose of Dicumarol has been administered on the evening before surgical intervention.[17] Because of the lag, this prophylaxis has not been effective on the day of and the days immediately following the operation. In a previous paper, a more effective Dicumarol prophylaxis during major surgery was proposed[1, 2] and this prophylaxis has since been carried out in about 100 patients predisposed to thromboembolism. This treatment is begun one to two weeks prior to the operation in order to get an idea of the patient's response to Dicumarol and to find the maintenance dose of Dicumarol. The prothrombin level on the day of operation must be above the bleeding limit (5 to 10 per cent), but must also lie in the therapeutic range. A standardized and sensitive method for the control of the therapy is therefore essential.

As most postoperative thromboembolic complications occur in the first 10 to 12 days after the operation, the anticoagulant prophylaxis should be maintained at least in this period, ideally 2 to 3 weeks and even longer in a case of atrial fibrillation.

Obviously, uncontrollable bleeding is the main risk of this procedure, but this has not occurred in this small group of patients.

Thromboembolic complications occurred among the control patients with the usual expected incidence, but none of the Dicumarol treated patients developed thrombotic diseases during the periods of treatment. Though the number of patients in the two groups is too small to allow a definite conclusion at the present time, our results as presented here have shown that an effective anticoagulant prophylaxis with Dicumarol can be maintained during mitral commissurotomy. The figures indicate that a considerable decrease in the number of postoperative thromboembolic incidents can be expected. The final evaluation of the therapy, here described, will have to wait for the treatment of a larger number of patients.

Summary

Mitral commissurotomy was performed on 26 patients under anticoagulant prophylaxis with Dicumarol. The operations were performed with a prothrombin level in the therapeutic range (10 to 30 per cent).

Hemorrhage during and after the operations was not greater in this group of patients compared with a control group (26 patients) studied at the same time or compared with 50 similar operations performed in previous years.

Although mitral commissurotomy predisposes to thromboembolic complications, during and after surgery, this had not occurred in the Dicumarol-treated group of patients. In the control group, these complications occurred just as frequently as expected (15 to 20 per cent of the cases). A larger group of patients is necessary before the effectiveness of this treatment can be finally evaluated.

Summario in Interlingua

Commissurotomia mitral esseva executate in 26 patientes sub prophylaxe anticoagulante a Dicumarol. Le operationes esseva executate a nivellos prothrombinic intra le limites therapeutic (10 a 30 pro cento).

Hemorrhagias durante e post le operationes non esseva plus frequente in iste gruppo de patientes que in un gruppo de 26 patientes de controlo qui esseva operate al mesme tempore o que in un gruppo de 50 patientes subjicite a simile operationes in previe annos.

Ben que commissurotomia mitral predispone le patiente a complicationes thromboembolic durante e post le intervention chirurgic, nulle tal complicationes ha occurrite in le casos del patientes tractate a Dicumarol. In le gruppo de controlo le frequentia de tal complicationes esseva de accordo con nostre expectationes (15 a 20 pro cento). Un plus grande numero de casos debe esser observate ante que le efficacia de iste tractamento pote esser definitivemente evalutate.

REFERENCES

[1] Müllertz, S. and Storm, O.: Anticoagulant therapy with Dicumarol maintained during major surgery. Circulation **10:** 213, 1954.

[2] Storm, O., Müllertz, S. and Tybjærg Hansen, A.: Anticoagulant Prophylaxis in Thoracic Surgery. *In*, Thrombose und Embolie, Proceedings of the I. International Conference, Th. Koller and W. R. Merz, eds. Basel, Schwabe, 1954, p. 959.

[3] Owren, P. A. and Aas, K.: The control af dicumarol therapy, and the quantitative determination of prothrombin and proconvertin. Scandinav. J. Clin. & Lab. Invest. **3:** 201, 1951.

[4] Astrup, T., Müllertz, S. and Hansen, J. R.: The value of Owren's method of estimating prothrombin. Scandinav. J. Clin. & Lab. Invest. **3:** 209, 1951.

[5] Bjerkelund, C. J.: The method of administering Dicumarol. Lancet **264:** 260, 1953.

[6] Geil, T., Lund, E., Dam, H. and Søndergaard, E.: Studies on the efficiency of vitamin K_1 in small doses as antidote against anticoagulants of the Dicumarol type. Scandinav. J. Clin. & Lab. Invest. **9:** 340, 1954.

[7] Baden, H. and Therkelsen, F.: Extra-auricular mitral valvulotomy. Thorax **9:** 340, 1954.

[8] Bigelow, W. G. and Greenwood, W. F.: Mitral stenosis with and without surgery. Surg. Clin. North America **875:** 1954.

[9] Bland, E. F., Scanell, J. G. and Myers, G. S.: Mitral commissurotomy and appendage amputation for recurring embolism. *In*, Thrombose und Embolie, Proceedings of the I. International Conference, Th. Koller and W. R. Merz, eds. Basel, Schwabe, 1954, p. 1178.

[10] Askey, J. M. and Cherry, C. B.: Thromboembolism associated with auricular fibrillation. J.A.M.A. **144:** 97, 1950.

[11] Wright, I. S., Beck, D. F. and Marple, C. D.: Myocardial infarction and its treatment with anticoagulants. Lancet **266:** 92, 1954.

[12] Wishart, J. H. and Chapman, C. B.: Dicumarol therapy in congestive heart failure. New England J. Med. **239:** 701, 1948.

[13] Owren, P. A.: Long-term Dicumarol Treatment in Cardiovascular Disease. Technique and Results. *In*, Thrombose und Emboli, Proceedings of the I. International Conference, Th. Koller and W. R. Merz, eds. Basel, Schwabe, 1954, p. 1085.

[14] Bailey, C. P., Olsen, A. K., Kown, K. and Nichols, H.: Commissurotomy for mitral stenosis. J.A.M.A. **149:** 1085, 1952.

[15] Warren, R.: Arterial embolism. Ann. Surg. **140:** 311, 1954.

[16] Baden, H.: In preparation.

[17] Kistner, R. W. and Smith, G.: A ten year analysis of thromboembolism and dicumarol prophylaxis. Surg., Gynec. & Obst. **98:** 437, 1954.

[18] Barker, N. W.: Anticoagulant Therapy. *In*, Thrombose und Emboli, Proceedings of the I. International Conference, Th. Koller and W. R. Merz, eds. Basel, Schwabe, 1954, p. 683.

Cardiovascular Collapse in Acute Poliomyelitis

By J. A. Hildes, M.D., M.R.C.P. (Lond.), F.R.C.P. (Canada), A. Schaberg, M.D., and A. J. W. Alcock, M.D.

Cardiovascular collapse accounted for approximately one-third of the deaths from acute poliomyelitis in two epidemics. This syndrome occurred early in the disease and only in cases of bulbar involvement. In all cases there was morphologic involvement of the medulla and in 75 per cent of the cases there was a varying degree of myocarditis. There was a much smaller incidence of less severe myocarditis in the cases dying of other causes. It is suggested that the combination of sustained vasoconstriction arising as a result of the medullary lesion and the presence of interstitial myocarditis leads to circulatory failure and pulmonary edema.

ALTHOUGH cardiovascular collapse had previously been noted in patients with acute poliomyelitis,[1, 2] Baker and his colleagues[3, 4] first indicated that this lethal symptom complex is a relatively common feature of bulbar poliomyelitis. They examined in detail the medulla of 80 cases dying of poliomyelitis and concluded that this syndrome was due to involvement of the large cells in the ventromedial reticular substance of the medulla.

There are also reports in the literature noting the occurrence of an interstitial myocarditis in poliomyelitis.[5-10] Electrocardiographic changes in a variable proportion of patients with acute poliomyelitis have also been reported.[6, 9] These reports do not record whether the histologic changes described by Baker and his associates[4] occurred in their cases. On the other hand, the reports by Baker and his colleagues[3, 4] deal mainly with the central nervous system findings.

Maloney and Whittenberger[11] suggested from their experiments on dogs that a high negative intratank pressure may play an important role in cardiovascular collapse in respirator patients by interfering with the return of blood to the heart, particularly if the circulation is failing.

In view of the uncertain role played by different factors in the etiology of this syndrome, it seemed worthwhile to review our cases of cardiovascular collapse.

From the Winnipeg Municipal Hospitals and the Department of Physiology and Medical Research, University of Manitoba, Winnipeg, Canada.

Case Material

During 1952 and 1953 a total of 1359 cases were admitted to the acute poliomyelitis wards of the Winnipeg Municipal Hospitals. Of these, 523 had bulbar involvement and there were 82 deaths in the whole series. The immediate cause of death in 22 cases was cardiovascular collapse (table 1). Autopsies were carried out on 20 of these 22 cases and on 47 of the remaining patients who died. The deaths of the latter were due to a variety of causes such as secondary bacterial infection, asphyxia and gastrointestinal ulceration.[12] Six patients, showing clinical evidence of this syndrome, survived (table 2).

All patients with any evidence of bulbar involvement were carefully followed clinically and a running record of blood pressure, pulse, temperature, respirations and state of consciousness was maintained. Cases coming to autopsy were examined completely in order to determine as accurately as possible the factors leading to the lethal outcome.

Clinical Syndrome

The syndrome of cardiovascular collapse is a complication of the early acute phase of bulbar poliomyelitis. All these patients had clinical evidence of pharyngeal involvement. This syndrome was not encountered in any of 640 patients with only spinal paralysis. Sixty-eight of these were respirator cases; there were five deaths and three postmortem examinations in this spinal group.

In the 22 cases shown in table 1, the average time from onset of illness to death was five days and the signs of cardiovascular collapse

TABLE 1.—*Fatal Cases*

Case	Sex & Age	Duration Bulbar Signs—Days	Max. Temp.	Respirator and/or Tracheotomy*	Blood Pressure Phases Duration in Hours			Duration of Noradrenaline†—Hours	Clinical Pulmonary Edema‡	Autopsy Findings§	
					Normal	Hypertensive	Hypotensive			Pulmonary edema	Myocarditis
1	F 21	1	—	—	—	—	10	—	+++	+++	++
2	F 19	2	101 F.	—	—	—	2	—	0	+	0
3	M 33	2	100 F.	—	—	—	<1	—	0	+++	+
4	M 8	<1	102 F.	—	—	—	1	—	+	+	++
5	M 10	<1	105 F.	—	—	—	6	2½	+++	No Autopsy	
6	F 27	2	106 F.	—	—	—	18	15	++	++	0
7	M 12	3	104 F.	—	<1	—	2	—	+	++	+
8	M 4	1	106 F.	R & T	10	—	1	—	0	0	+
9	F 15	2	103 F.	—	36	—	3	1	+	+	+++
10	M 44	2	—	T	12	—	5	5	+++	+++	+
11	M 35	2	103 F.	T	13	—	8	8	+++	No Autopsy	
12	F 35	2	105 F.	R	17	—	27	27	0	++	+
13	F 21	2	102 F.	—	29	—	7	4	0	++	+++
14	M 15	4	104 F.	—	75	—	<1	—	0	+	0
15	F 29	<1	108 F.	R	24	—	3	2½	0	++	0
16	M 27	<1	102 F.	—	—	1 (190/150)	1	—	+++	+++	0
17	M 29	2	106 F.	R & T	—	2 (154/124)	4	1½	0	++	++
18	F 17	1	104 F.	R & T	4	2 (160/?)	25	25	+++	++	+++
19	F 11	1	106 F.	—	5	2 (210/130)	4	4	0	+	0
20	M 15	<1	105 F.	—	6	3 (170/?)	10	9	+++	+++	+++
21	M 40	<1	100 F.	—	2	3 (170/?)	<1	—	0	++	++
22	M 30	2	104 F.	—	28	2 (165/?)	26	25	+++	++	+++

* This refers to the use of the tank respirator and/or tracheotomy prior to onset of the cardiovascular collapse. Cases 1, 5, 6, 10, 13, 19, 20, 22 went into respirators some time after that and, similarly, cases 1, 5, 6, 12, 15, 22 had tracheotomies later.

† The dose of noradrenaline was adjusted to try and maintain systolic pressure above 100 mm. Hg.

‡ Lesser grades of pulmonary edema, as evidenced by basal crepitations, were often not detected since the chest was not always examined serially.

§ Graded as indicated in the text.

almost always occurred within 48 hours of the first evidence of bulbar paralysis which, however, was not always extensive or severe. The patients were usually alert, exceedingly apprehensive and agitated. Body temperature was recorded at 104 F. or over in approximately half the cases. The pulse rate was fast during the stage of shock and often difficult to feel at the wrist, but always regular.

In table 1, the cases have been arranged according to the blood pressure findings. In cases 1 to 6, systolic pressure was below 80 mm. Hg when first recorded. Cases 16 and 17 were hypertensive on admission. The remaining cases were normotensive on admission; cases 7 to 15 remained so until their blood pressure fell, but the last four cases in the table developed transient hypertension before the stage of shock. The fall in blood pressure was sometimes precipitous but in others it fell over a period of hours. In the shock stage, the extremities were cold and clammy and mottled with peripheral grey cyanosis.

Gross clinical pulmonary edema was a notable feature in more than a third of the cases. In two of these (cases 18 and 22), who survived for several hours after the onset of pulmonary edema, the autopsy findings suggested some regression of the pulmonary edema before death. A rapidly fatal termination within a few hours was more the rule. Of the 22 cases, 5 were in respirators and five had tracheotomies at the time of the onset of the cardiovascular collapse. It can be seen from table 1 that 13 of the 22 cases were given continuous infusions of noradrenaline with variable results. It seemed of definite but temporary

TABLE 2.—*Survivors*

Case	Sex & Age	Duration Bulbar Signs—Days	Max. Temp.	Respirator and/or Tracheotomy*	Blood Pressure Phases Duration in Hours			Duration of Noradrenaline—Hours*	Clinical Pulmonary Edema*	Final Results
					Normal	Hypertensive	Hypotensive			
23	F, 28	2	103 F.	R & T	48	—	20	40	0	Died 6 months later. Cause undetermined.
24	F, 26	1	104 F.	R	20	—	?24	24	+++	Died 3 months later. Secondary infection.
25	M, 26	4	106 F.	R & T	—	96 (170/?)	6	6	0	Remains with severe spinal paralysis.
26	M, 19	3	103 F.	R & T	—	24 (195/?)	?48	46	0	Remains with severe spinal and respirator paralysis.
27	M, 20	2	102 F.	—	—	46 (220/115)	12	—	0	Discharged in 6 weeks. Moderate bulbar, mild spinal. Normotensive.
28	M, 29	1	102 F.	—	—	12 (178/116)	96	24	0	Discharged in 6 weeks. Mild bulbar paralysis. Normotensive.

* See footnotes to table 1.

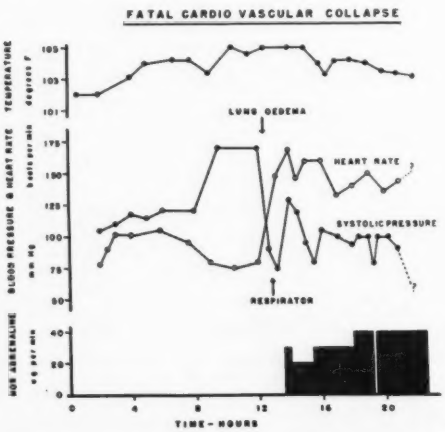


FIG. 1. Record of rectal temperature, heart rate, systolic blood pressure and dose of noradrenaline throughout the hospital course of case 20 (table 1).

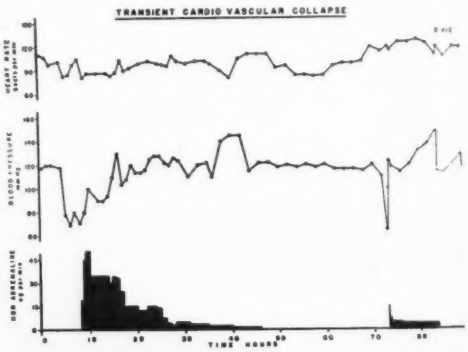


FIG. 2. Record of pulse rate, systolic blood pressure and dose of intravenous noradrenaline during the episodes of hypotension in case 23 (table 2).

benefit in six of these cases and in five of the survivors shown in table 2.

A typical example of the fulminating course is illustrated in figure 1.

There were a few cases amongst the remaining patients who died from bulbar poliomyelitis which showed some features of this syndrome, both clinically and pathologically; for example, a sharp drop in blood pressure and post-mortem evidence of pulmonary edema. These may have been examples of the same syndrome but at autopsy other causes of death were found and they have been excluded from this series.

Table 2 shows six patients who recovered from an attack of hypotension. The duration of the low blood pressure phase was sometimes difficult to assess when the patient had an infusion of noradrenaline. If the blood pressure was maintained when the infusion was temporarily stopped, the drug was discontinued. Such a test is illustrated in figure 1.

The clinical course of case 23 is illustrated in figure 2. She developed ascending spinal paralysis requiring respirator treatment. The next day a

tracheotomy was necessary for bulbar paralysis. On the day following the tracheotomy she became extremely apprehensive and had the episodes of hypotension treated with noradrenaline as shown in the figure. Following this, she remained well but severely paralyzed. She could neither swallow nor breathes. Six months later she suddenly convulsed, became unconscious and died a few days later. The central nervous system at autopsy showed marked loss of lower motor neurones in all areas as well as severe involvement of the medullary reticular substance. The heart was grossly and microscopically normal. Terminal partial atelectasis of a few hours' duration involved both lungs. The cause of death was not apparent.

Case 24 survived a severe episode of pulmonary edema but also died a few months later. On admission she had rapidly ascending spinal paralysis and went into a tank respirator. Within two hours she suddenly developed gross pulmonary edema and cyanosis. She remained alert and very apprehensive. A bronchoscope was immediately passed to facilitate removal of the frothy edema fluid and to deliver a high concentration of oxygen deep into the air passages. She was given 0.2 mg strophanthin and also a small dose of sodium pentothal to allay her apprehension. The pulmonary edema subsided in half an hour and the bronchoscope was removed after tracheotomy had been performed. Following this episode her systolic blood pressure was 100 and her pulse rate 140. The following day her systolic blood pressure fell to 80 and was returned to between 90 and 100 with an infusion of noradrenaline which was continued for 24 hours. Three days later tracheal obstruction produced a sudden fall in systolic blood pressure to 60 but this rose again a few minutes after the obstruction was relieved. During the following weeks she remained in a state of chronic ill health and she succumbed three months later to bronchopneumonia and pyopneumothorax. Autopsy examination was not allowed.

The other four survivors had not so severe a clinical course.

Cases 25 and 26 were also in respirators at the onset of cardiovascular collapse. The former was given 0.25 mg. strophanthin intravenously when his systolic blood pressure fell to 90. Following this the blood pressure remained at 110 for several hours but then fell to 75 and his pulse rate rose to 170. An intravenous infusion of noradrenaline raised the blood pressure to 105 and the pulse rate slowed to 140. His course thereafter was uneventful but he has remained severely paralyzed. When case 26 developed a rapid pulse, falling blood pressure and sweating collapse, he was given intravenous strophanthin, intravenous Digoxin and oxygen without apparent effect. However, his blood pressure was elevated to 100 systolic by intravenous noradrenaline. This was continued for two days, after which blood pressure remained normal.

Cases 27 and 28 developed this shock syndrome without being in respirators although the former patient developed respiratory insufficiency shortly afterwards. His blood pressure recovered spontaneously. The blood pressure in case 28 was maintained for a day with noradrenaline. When it was discontinued his systolic blood pressure remained between 80 and 90 mm. Hg. He seemed so well and was without the cold, clammy peripheral cyanosis or the apprehension seen in the fatal cases that the drug was discontinued. He made steady improvement; his blood pressure finally came back to normal and at the time of discharge he was left with very little residual paralysis.

The occurrence of hypertension in these patients is of some interest. Six of the fatal cases (table 1) and four of those who survived (table 2) had hypertension prior to the onset of hypotension. There were other patients, not shown in the tables, who were probably examples of the same syndrome without the development of the hypotensive phase. One example will serve to illustrate this.

A 16-year old boy was admitted with a five-day history of illness and with pharyngeal and palatal paralysis of one day's duration. Temperature was 102 F. pulse 120 and respirations 25. Systolic blood pressure was 130. During the next two days his bulbar paralysis worsened but he developed practically no spinal paralysis. His blood pressure rose to 190/120. He became extremely agitated but remained quite alert. Temperature and pulse rate began slowly to subside to normal and by the eighth hospital day swallowing function began to recover and the patient felt quite well. However, his blood pressure, which had reached a height of 220/130, remained elevated above normal for 10 days, during this time it gradually subsided. At the time of discharge, three weeks after admission, his blood pressure was 125/70 and there was moderate residual weakness of the face and palate.

Pathology

The postmortem findings of the 20 cases autopsied are summarized in table 1. The main abnormal findings were limited to the central nervous system, the heart and the lungs. A few of these patients had clinically insignificant lesions of the upper gastrointestinal tract.[12] There was no pathologic evidence of airway obstruction, bacterial infection or hemorrhage.

The lungs showed a varying degree of acute pulmonary edema in all but one case.

FIG. 3. Sections of heart muscle showing interstitial myocarditis in case 9 (table 1). Haematoxylin-eosin stain x 340.

Involvement of the Brain Stem: The following areas were examined histologically: lumbar, low thoracic, high thoracic and cervical cord; the medulla at four levels; the pons at two levels; the substantia nigra; the hypothalmus at the levels of the mamillary bodies, tuber cinereum and optic chiasma; the basal nuclei and the motor cortex. In all 20 patients, there was medullary involvement, varying from mild neuronal damage and interstitial inflammatory reaction to diffuse involvement with focal destruction of tissue. Although the region between the floor of the fourth ventricle and the olivary nucleus in the upper part of the medulla was one of the most severely involved areas, there was, as far as our examination went, no apparent difference between the patients dying of cardiovascular collapse and those in which death was attributed to other causes.[12] With respect to the other areas examined, the patients without cardiovascular collapse appeared to have a somewhat smaller incidence of involvement of the cerebellum and the hypothalmus. The motor cortex was involved in only a few cases in both groups.

Involvement of the Myocardium: The gross examination of the heart was usually normal although in two cases the heart muscle was considered abnormally flabby. The average heart weight was approximately 10 per cent greater than normal. This has been previously described.[8]

In 14 of the 20 cases autopsied, there was histologic evidence of myocarditis. Blocks for microscopic examination were taken from the anterior and posterior wall of the left ventricle, the septum and the pulmonary conus. The lesions are graded in table 1 as mild, moderate or severe. We considered lesions, mainly limited to perivascular spaces, to be mild. Those which also showed scattered focal lesions in the myocardium were considered to be moderately severe. Diffuse involvement was considered to be a severe grade. The exudate consisted of lymphocytes, plasma cells, macrophages and polynuclear cells, the latter predominating in the more severe cases (fig. 3). Although the majority of the muscle fibers were usually spared, there was often involvement of a few fibers adjacent to the lesion. These fibers were swollen, fragmented, had lost their striations and showed a granular cytoplasm. Some of the fibers showed cloudy swelling and a tendency to coalesce with adjacent fibers.

Among the other 47 postmortem examinations for poliomyelitis, where the cause of death was asphyxia, gastrointestinal hemorrhage or secondary infection, 12 hearts showed a mild degree of inflammatory reaction and five had septic abscesses in the myocardium as well as in the other organs. Four of the 12 were in cases dying of septicemia and it is difficult to distinguish between a mild septic reaction and a virus inflammation in these cases. In none of these cases was the inflammatory reaction severe or moderately severe as it was in nine of the 14 cases showing myocarditis and who died with the syndrome of cardiovascular collapse.

DISCUSSION

Several mechanisms could be responsible for inducing cardiovascular collapse in polio-

myelitis. From the data presented, some of these can be excluded as primary factors in our cases.

Destruction of the vasomotor center was considered responsible by Baker and coworkers.[4] Such a lesion should lead to a general absence of sympathetic activity with postural hypotension. Although measurements of blood flow were not made, it was clinically obvious that our patients had intense vasoconstriction of the skin at least. Symptoms were not alleviated by tilting the head down. Histologically, the area of the reticular substance in the medulla was involved in all or our cases and no case of this syndrome was found in patients with spinal involvement only. The medullary area was also involved in cases dying of other causes. But death in such cases occurred at a somewhat longer interval after the onset of paralysis than did cardiovascular collapse.

Myocarditis was more common and also more severe in the cases dying of cardiovascular collapse compared with other bulbar cases coming to autopsy. It is difficult to envision a virus myocarditis limited only to cases with bulbar poliomyelitis. Indeed, electrocardiographic evidence indicates that spinal and nonparalytic cases may also have transient myocardial changes.[6, 9] From these considerations and also from the fact that one-fourth of the cases did not show myocarditis, it seems unlikely that the heart lesion is the basis for this syndrome although its presence would probably aggravate it.

It has been suggested[13] that all deaths from acute poliomyelitis can be attributed to hypoventilation. It is difficult to categorically deny this on our evidence. We have seen patients, other than those reported here, in terminal shock from airway obstruction. However, the majority of the present patients were not in respiratory distress at the onset of the collapse; nor were there any indications at postmortem examination of airway obstruction or asphyxia from other causes.

Unfortunately, arterial puncture for blood gas analysis was carried out only on two of these patients during the phase of shock. Case 27 (table 2) did have a moderate respiratory acidosis (carbon dioxide partial pressure 77 mm.; pH 7.28); case 12 (table 1) had a normal arterial carbon dioxide partial pressure (45 mm.) a few hours before death although the blood pH was 7.32. Many other cases with airway obstruction were seen with severe acidosis which promptly recovered when ventilation was returned to normal.[14]

The undesirable effects on the circulation of prolonged positive pressure breathing are well known.[11, 15, 16] However, as only five of our patients were in respirators at the onset of cardiovascular collapse, this is unlikely to be a factor of prime importance in our cases.

Severe hyperthermia may be lethal. Approximately half of the fatal cases had fever with rectal temperatures of 104 F. or over. It is not considered likely that such a mortality rate would result from comparable body temperatures in other infectious diseases.

Although there is no reason to suspect acute adrenal insufficiency in poliomyelitis, the occurrence of lethal shock made us consider this possibility. The adrenal glands at autopsy in some cases showed a varying degree of histologic change characteristic of stress.[17, 18] There was no difference in the appearance of the glands between the cases dying of cardiovascular collapse and the remaining 47 cases autopsied.

The transient hypertension of six of the fatal cases and four of the six surviving cases, as well as other cases without cardiovascular collapse, may indicate that severe vasoconstriction may be an important factor leading to heart failure and pulmonary edema.[19, 20] Such a postulated mechanism would be greatly enhanced by an already weakened myocardium from viral myocarditis. Although we have no direct evidence to support this hypothesis, it is put forward as the suggested mechanism in our cases as it seems to best fit the clinical and pathologic data. Further investigation along these lines would be very helpful in confirming or refuting this suggestion.

On the basis of this tentative hypothesis about the mechanism of this syndrome, one would expect that vasoconstrictor drugs would be of no benefit in treatment. Indeed, animal experiments[21] suggest that such therapy may actually be harmful in spite of temporary im-

provement in blood pressure and clinical appearance. Despite this, the use of noradrenaline seemed to be of definite benefit in some of our cases. In others, although it temporarily elevated the blood pressure, it appeared to have no beneficial influence on the course of the disease. Of the surviving cases shown in table 2, noradrenaline seemed an important factor in case 23. Case 24 was most gravely ill when she had pulmonary edema; she recovered from this before she was given noradrenaline. None of the other four survivors at any time seemed as critically ill as the fatal cases. We attribute their survival more to a mild form of the syndrome rather than to the therapy.

From the experimental work on animals,[22, 23, 24] the use of hypotensive drugs in the early hypertension phase might be of value. However, we have no experience with this possible method of treatment.

Summary

(1) A series of 22 fatal cases and 6 surviving cases of cardiovascular collapse in acute poliomyelitis is reported.

(2) Clinically, the syndrome came on acutely within 1 or 2 days after the onset of bulbar paralysis. It was characterized by apprehension, hyperthermia, fast regular pulse and was sometimes preceded by a short period of hypertension. It then progressed to a state of shock with cold, sweating and cyanosed extremities. Pulmonary edema was a common terminal feature.

(3) At autopsy, there was involvement of the medulla in all cases and pulmonary edema in all but one case. Interstitial myocarditis was found in 75 per cent of the cases.

(4) Treatment with noradrenaline appeared to be of benefit in some cases but this was usually transient. Four of the six surviving cases had a mild form of the syndrome.

(5) It is suggested that the mechanism for the syndrome is a combination of vasoconstriction resulting from a medullary lesion and a viral myocarditis. This leads to acute heart failure and pulmonary edema.

Addendum

Since these cases were studied we have only once encountered this syndrome. The blood pressure of an adult male, admitted with acute bulbar poliomyelitis, was 170/100 and pulse rate was 90. He rapidly deteriorated, became agitated and somewhat disoriented and 14 hours after admission was cold and clammy; the blood pressure could not be recorded; his heart rate had risen to 160. Rather than increasing his blood pressure, a hypotensive agent, Arfonad,* was given by continuous intravenous infusion for 26 hours at a rate which maintained the systolic blood pressure between 70 and 80 and the diastolic between 60 and 65. His color and general condition improved markedly. When the drug was stopped his blood pressure remained normal although at the present time he is still in the acute stage of his disease.

This single case seems to corroborate the discussion above but further experience is obviously necessary before conclusions can be drawn.

Acknowledgments

The technical assistance of Miss K. Nagy and Mrs. E. Pullen is gratefully acknowledged.

Summario in Interlingua

Collapso cardiovascular esseva responsabile pro circa duo tertios del mortes in duo epidemias de poliomyelitis acute. Iste syndrome occurreva tosto in le curso del morbo e solmente in casos de involvimento bulbar. In omne casos il habeva un involvimento morphologic del medulla, e in 75 pro cento del casos varie grados de myocarditis esseva observate. Le frequentia e le severitate de myocarditis esseva multo minus extense inter le casos de mortes per altere causas. Nos presenta le hypothese que le combination de (1) vasoconstriction continue resultante del lesion medullar e (2) le presentia de myocarditis interstitial es le causa de disfallimento circulatori e edema pulmonar.

REFERENCES

[1] Nordmann, M. and Muller, O.: Über die Lage eines Blutdruckregulierenden Zentrums in der Medulla Oblongata. Klin. Wchnschr. **11:** 1371, 1932.

[2] Smith, E. and Fineberg, H. I.: Bulbar poliomyelitis and its treatment. J. Paediat. **4:** 590, 1934.

[3] Brown, J. R. and Baker, A. B.: Poliomyelitis I. Bulbar poliomyelitis; a neurophysiological interpretation of the clinicopathological findings. J. Nerv. & Ment. Dis. **109:** 54, 1949.

* Trimethaphan camphor sulfonate from Hoffmann-LaRoche.

[4] Baker, A. B., Matzke, H. A. and Brown, J. R.: Poliomyelitis III. Bulbar poliomyelitis: a study of medullary function. Arch. Neurol. & Psychiat. **63:** 257, 1950.

[5] Saphir, O. and Wile, S. A.: Myocarditis in poliomyelitis. Am. J. M. Sc. **203:** 781, 1942.

[6] Gefter, W. I., Leaman, W. G. Jr., Lucchesi, P. F., Maher, I. E. and Dworin, M.: The heart in acute anterior poliomyelitis. Am. Heart. J. **33:** 228, 1947.

[7] Dolgopol, V. B. and Cragan, M. D.: Myocardial changes in poliomyelitis. Arch. Path. **46:** 202, 1948.

[8] Ludden, T. E. and Edwards, J. E.: Carditis in poliomyelitis; an anatomic study of thirty-five cases and review of the literature. Am. J. Path. **25:** 357, 1949.

[9] Laake, H.: Myocarditis in poliomyelitis. Acta. med. scandinav. **140:** 159, 1951.

[10] Teloh, H. A.: Myocarditis in poliomyelitis. Arch. Path. **55:** 408, 1953.

[11] Maloney, J. V., Jr., and Whittenberger, J. L.: Clinical implications of pressures used in the body respirator. Am. J. M. Sc. **221:** 425, 1951.

[12] Schaberg, A., Hildes, J. A., and Alcock, A. J. W.: Upper gastrointestinal lesions in acute bulbar poliomyelitis. Gastroenterology **27:** 838, 1954.

[13] Christie, A. B.: Respiratory failure in the acute case of poliomyelitis. Brit. M. J. **2:** 663, 1954.

[14] Thomson, A. E.: Unpublished data.

[15] Werko, L.: The influence of positive pressure breathing on the circulation in man. Acta. med. scandinav. **128:** Suppl. 193, 1947.

[16] Sarnoff, S. J. and Case, R. B.: Pharmacologic support of the circulation during positive pressure breathing. Federation Proc. **14:** 130, 1955.

[17] Rich, A. R.: A peculiar type of adrenal cortical damage associated with acute infections, and its possible relation to circulatory collapse. Bull. Johns Hopkins Hosp. **74:** 1, 1944.

[18] Schaberg, A.: Bijnierschors en Ziekte. Leiden, H. E. Stenfert Kroese, 1951.

[19] Wang, S. C. and Overman, R. R.: A neurogenic factor in experimental traumatic shock: a summary of recent studies including observations on procainized and spinal dogs. Ann. Surg. **129:** 207, 1949.

[20] Sarnoff, S. J., and Sarnoff, C. L.: Neurohemodynamics of pulmonary edema. I. Autonomic influence on pulmonary vascular pressures and the acute pulmonary edema state. Dis. Chest. **22:** 685, 1952.

[21] Remington, J. W., Hamilton, W. F., Boyd, G. H., Jr., Hamilton, W. F., Jr. and Caddell, H. M.: Role of vasoconstriction in the response of the dog to hemorrhage. Am. J. Physiol. **161:** 116, 1950.

[22] Wiggers, H. C., Goldberg, H., Roemhild, F. and Ingraham, R. C.: Impending hemorrhagic shock and the course of events following administration of dibenamine. Circulation **2:** 179, 1950.

[23] Sarnoff, S. J., Berglund, E., and Sarnoff, C. L.: Neurohemodynamics of pulmonary edema. III. Estimated changes in pulmonary blood volume accompanying systemic vasoconstriction and vasodilation. J. Applied Physiol. **5:** 367, 1953.

[24] Baez, S., Zweifach, B. W., and Shorr, E.: Protective action of dibenamine against the fatal outcome of hemorrhagic and traumatic shock in rats. Federation Proc. **11:** 7, 1952.

Pulmonary Stenosis and Ventricular Septal Defect with Arteriovenous Shunts

A Clinical and Hemodynamic Study of Eleven Patients

By JOHN A. CALLAHAN, M.D., ROBERT O. BRANDENBURG, M.D. AND H. J. C. SWAN, M.B., Ph.D., M.R.C.P. (LOND.)

Patients who have pulmonary stenosis and ventricular septal defect usually have a right-to-left intracardiac shunt. This paper presents hemodynamic and clinical data on 11 patients who have pulmonary stenosis, ventricular septal defect and left-to-right shunts. Four of these patients also have defects in the atrial septum, and three have demonstrable bidirectional shunts. The level and direction of shunts were determined by blood oxygen-saturation data and indicator-dilution studies. Choice of the form of treatment to be used in patients such as these should be based largely on hemodynamic considerations. Many resemble patients with tetralogy of Fallot who have had a successful pulmonary valvotomy.

IN patients who have stenosis of the pulmonary valve or outflow portion of the right ventricle and a ventricular septal defect, blood is usually shunted through the defect to the left ventricle or the aorta. Recent publications have called attention to a group of patients who have pulmonary stenosis and ventricular septal defect without cyanosis, in whom the blood is shunted from left to right (arteriovenous) through the defect.[1-3]

It is the purpose of this paper to present hemodynamic and clinical data in seven cases of pulmonary stenosis and ventricular septal defect in which a left-to-right shunt was the major hemodynamic anomaly and in four cases of pulmonary stenosis with both atrial and ventricular septal defects, all of which had left-to-right shunts but three had right-to-left (venoarterial) shunts in addition. Two of the first group of patients had been previously reported by Broadbent and associates.[2]

The patients were studied by cardiac catheterization, employing the method of Cournand and Ranges[4] as modified in apparatus and technics by Wood and associates.[5-7] The methods of analysis used have been described in greater detail in a recent paper by the present authors.[8]

From the Mayo Clinic and Mayo Foundation, Rochester, Minn. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

Abridgment of portion of thesis submitted by Dr. Callahan to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

ARTERIAL INDICATOR-DILUTION CURVES

Because of the value of indicator-dilution curves in the definition of normal and abnormal circulatory states, a statement outlining the principles which are the basis for the use of dilution curves in the study of congenital heart disease with intracardiac and intravascular shunts is appropriate. The changing concentration of an indicator with time, at the sampling site in the arterial system, defines a contour which depends to a major extent on the pathway or pathways taken by the indicator from the injection site to the sampling site. Dilution curves do not define defects as such but indicate the nature of pathways of blood flow, normal or abnormal. Two distinct and fundamental dilution patterns are associated with the presence of a right-to-left and of a left-to-right shunt respectively.[9] When a right-to-left shunt exists, a portion of the injected dye traverses the defect and reaches the systemic arterial sampling site before that portion of the injected dye which passes through the pulmonary circulation. The resultant dilution curve is characterized by a short appearance time and an abnormal initial deflection which is proportional to the amount of dye shunted and hence to the volume of the shunt.[10] When a left-to-right shunt is present, the blood follows a normal pathway through the lungs, but then a part of the blood is

shunted to recirculate through the pulmonary vessels. In this situation the appearance time and the slope of increasing dye concentration of the dilution curve are normal. The magnitude of the peak of dye concentration is reduced in comparison to normal, and the concentration of dye at the sampling site declines slowly because with each recirculation of the indicator remaining in the pulmonary circulation, a constant fraction of the dye passes into the systemic circulation.[11] The site of injection of the dye is important in the localization of a shunt. Since the dye follows the pathway taken by the blood, a shunt will be defined only if it occurs at or beyond the site of injection of the dye. Injections of dye into different locations in the heart and great vessels frequently permit the localization of a defect through which a shunt is occurring.[12]

Clinical Data

The clinical data are summarized in table 1. Representative roentgenograms of the chest are reproduced in figure 1.

Table 1—*Clinical Data in 11 Cases of Pulmonary Stenosis With Left-to-Right Intracardiac Shunts*

	Group I: Pulmonary stenosis and ventricular septal defect*							Group II: Pulmonary stenosis, atrial and ventricular septal defects			
	1	2	3	4	5	6	7	1	2	3	4
Age, year	38	27	3	30	5	12	28	9	24	4	6
Sex	F	M	F	F	M	F	M	M	F	M	F
Effort dyspnea and fatigue (grade 0–4)†	2	1	1	3	3	1?	1	1	3	3	2
Cyanosis (grade 0–4)† since	0	0	0	0	1, 1 yr.	0	0	1, birth	1+, birth‡	0	2, 5 yr.‡
Systolic murmur 2nd and 3rd space	Gr. 4 with thrill	Present with thrill (louder right than left)	Gr. 3 with thrill	Gr. 3 left 5th space with thrill	Gr. 3 with thrill	Gr. 4 with thrill	Present with thrill	Gr. 2 with thrill	Gr. 3 with thrill	Gr. 4 with thrill	Gr. 3 with thrill
Other murmur	0	Diastolic lower left sternum	Gr. 1 diastolic pulmonary area	0	0	Diastolic pulmonary area	Diastolic pulmonary area	0	0	Gr. 2 diastolic 3rd and 4th space	0
Second sound	Faint, single	Split and accent.	Indistinct, not split or accent.	Single	Single	Accent.	Absent	Accent.	Accent. but single	Single	Absent
Heart enlargement (grade 0–4)†	0	2	2	3	1	2	2	0	1	3	2
Pulmonary arterial shadow (grade 0–4)†	2	2	3	2	2	2	0	0 (right-sided aorta)	1	4	0
Pulmonary vascular markings	Normal	Increased	Increased	Slight increase	Normal	Increased	Normal	Decreased	Normal	Normal	Normal

* Patients 4 and 6 were reported in a previous study.[2]

† Severity of symptoms and physical signs graded on a 0 (absent) to 4 (severe or marked) basis.

‡ Clubbing present.

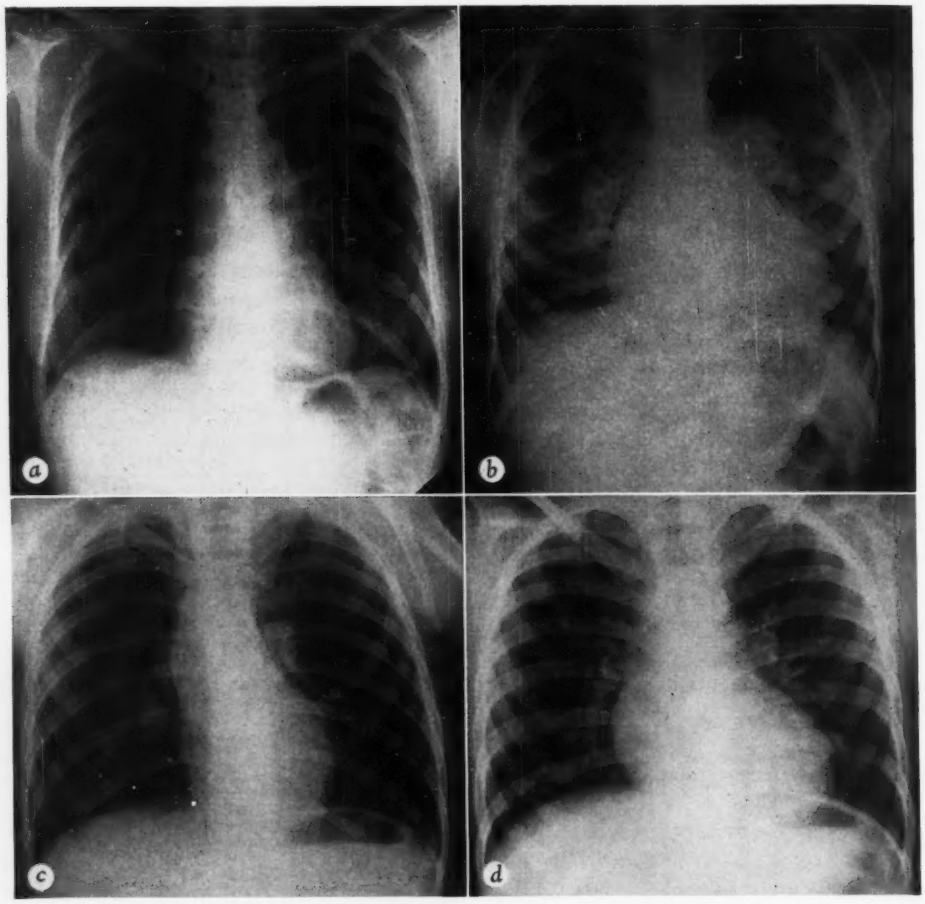


FIG. 1. Posteroanterior roentgenograms *a* and *b*. Patients 1 and 3, group I. The pulmonary arterial shadow is increased in both patients but particularly in patient 3 (1*b*). The vascular lung markings are markedly increased in patient 3 (1*b*) but are normal in patient 1 (1*a*). *c* and *d*. Patients 1 and 4, group II. There is concavity in the region of the pulmonary arterial shadow in both patients and a right-sided aortic arch in patient 1 (1*c*).

The most characteristic physical finding was a loud systolic murmur in the pulmonic area associated with a thrill. In some of the patients, murmurs were noted in other locations. The second heart sound in the second and third left intercostal spaces was absent, single or not accentuated in most of these patients.

The main pulmonary arterial shadow in the postero-anterior roentgenogram of the chest was increased in all patients except patient 7, ni whom it could not be definitely identified. The pulmonary vascular markings were considered to be normal in patients 1, 5 and 7 and increased in patients 2, 3, 4 and 6.

The electrocardiogram in patient 1 disclosed minimal electrocardiographic evidence of delayed activation of the right ventricle (R wave in aV_R). In patient 2 there was atrioventricular dissociation with auricular fibrillation. The electrocardiograms in patients 3 and 7 were interpreted to show evidence of biventricular hypertrophy. The electrocardiograms in patients 4 and 6 showed the configuration of right bundle-branch block in lead V_1 (partial right

TABLE 2.—*Intracardiac Pressures, Arterial Oxygen-Saturation Data, Blood Flow and Shunt Values in Seven Cases of Pulmonary Stenosis and Ventricular Septal Defect With Left-to-Right Shunt*

Case	Pressure, mm. Hg					% oxygen saturation breathing air			Arterial oxygen,* physical solution, vols. per 100 cc.	Blood flow index, L/min./M.²		L-R shunt, per cent of pulmonary flow
	PT	RV outflow	Low RV	RA	Radial artery	Mixed venous blood	Pulmonary artery	Radial artery		Pulmonary	Systemic	
1	18/5	52/4	52/4	8/2	139/71	75	81	97	1.0	3.9	3.0	25
2	46/18	48/2	95/2	11/3	150/84	80	89	96	1.8	7.5	4.9	35
3†	31/12	63/9	73/3	7/2	120/67	69	82	95	1.6	7.2	4.0	45
4	20/6	97/7	104/7	11/7	105/59‡	68	86	96	1.3	6.5	3.4	45
5†	31/12	55/2	90/3	6/3	95/69	63	77	98	1.9	4.3	2.2	50§
6	48/17	50/3	85/2	11/4	109/60	79	89	97	—	11.1	5.5	50
7	25/11	26/1	91/1	13/8	198/38	75	87	99	2.1	6.1	2.4	60

* Oxygen content minus oxygen capacity when breathing 100 per cent oxygen.
† Patient studied under anesthesia.
‡ Radial and right ventricular pressures not measured simultaneously.
§ Small right-to-left shunt found by dye dilution studies.

bundle-branch block in the latter, with evidence of left ventricular hypertrophy). In patient 5 there was evidence of right ventricular hypertrophy.

The patients in group II were quite similar to those in group I on clinical grounds, except that three of the patients in group II had cyanosis and two had clubbing of the fingers.

The pulmonary arterial shadow was increased in two patients and normal in two. One of the patients in whom the pulmonary arterial shadow was normal was found to have a right-sided aortic arch. The pulmonary vascular markings were normal in three patients and decreased in one.

The electrocardiogram in patient 1 showed no definite evidence of ventricular hypertrophy. In patients 2 and 4 there was electrocardiographic evidence of right ventricular hypertrophy. In patient 3 there was the pattern of right bundle-branch block and left ventricular hypertrophy.

HEMODYNAMIC DATA

Pulmonary Stenosis and Ventricular Septal Defect (*table 2*). The seven patients with pulmonary stenosis and ventricular septal defects were found to have arterial oxygen saturations of systemic arterial blood within the range of normal, while at rest, breathing air. The average arterial oxygen saturation in these patients, measured by the method of Van Slyke, was 97 per cent (range 95 to 99 per cent). In all but one of these patients, the arterial oxygen saturation was determined while the patient breathed 100 per cent oxygen. The average quantity of oxygen in physical solution (oxygen content minus oxygen capacity) found in arterial blood when 100 per cent oxygen was breathed was 1.6 volumes per 100 cc. of blood (range 1.0 to 2.1 volumes per cent). Under this circumstance, patient 1 was found to have 1.0 volume of oxygen per 100 cc. of blood in physical solution, which is below the range defined by Wood[13] for normal subjects, but the arterial oxygen saturation was within normal limits when this patient breathed air. It is unlikely that there was a significant right-to-left shunt in this patient because of the wide difference between systemic arterial and right ventricular systolic pressures. Also an arterial indicator-dilution curve obtained following injection of T-1824 into the right ventricle while the patient exercised failed to show evidence of a right-to-left shunt.* In patient 5, on the other hand, there was evidence by indicator-dilution curves of a

* Identification of small right-to-left shunts on the basis of minor degrees of desaturation of the systemic arterial blood is limited by the range of variability of arterial saturation encountered in normal subjects of from 94 to 101 per cent by Van Slyke analysis. It is possible for a 15 to 20 per cent right-to-left shunt to exist in the presence of an arterial oxygen saturation within the range of normal. Indicator-dilution curves have proved a more sensitive and a more certain method of diagnosis.[14]

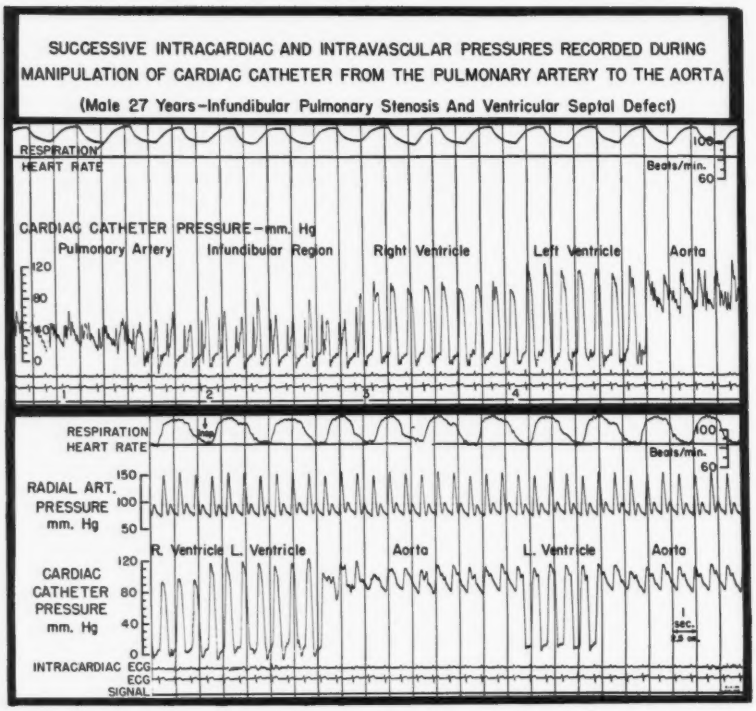


FIG. 2. Section of photographic record from the cardiac catheterization of patient 2, group I. In the upper panel the tip of the cardiac catheter was withdrawn successively from the pulmonary artery (1), through a zone of infundibular stenosis (2), into the right ventricle (3) and then advanced through the ventricular septal defect (4) into the left ventricle and into the aorta. This record is indicative of the presence of a normal pulmonary valve and of infundibular pulmonary stenosis. Note the gradient in pressure between the right and left ventricles and the change in the electrocardiogram recorded from the tip of the cardiac catheter as it crosses the ventricular septal defect. In the lower panel, pressures were recorded successively in the right ventricle, left ventricle and aorta and simultaneously in the radial artery. Note that the radial arterial systolic pressure exceeds the simultaneously recorded aortic, systolic pressure.

small right-to-left shunt at ventricular level but 1.9 volumes of oxygen per 100 cc. of blood were present in physical solution when the patient breathed 100 per cent oxygen.

The right ventricular systolic pressure was elevated above normal levels in each patient. The average right ventricular systolic pressure was 88 mm. of mercury (range: 52 to 120 mm.) and the radial arterial systolic pressure exceeded the right ventricular systolic pressure in each case. All but one of the measurements were obtained from simultaneous records of radial arterial and right ventricular pressures (fig. 2). The average difference between systolic pressures in the radial artery and the right ventricle was 41 mm. of mercury.*

The pulmonary arterial pressure was elevated above the normal range in some of the patients in group I. The average pulmonary arterial systolic pressure was 32 mm. of mercury (range: 18 to 48 mm.).

* A comparison of radial arterial and right ventricular systolic pressures does not necessarily reflect the pressure gradient between the right and left ventricles. Kroeker and Wood[15] found that in 12 normal male subjects, the peripheral arterial systolic pressure uniformly exceeded the aortic systolic pressure generated by the same heartbeat. The average radial systolic pressure was 112 per cent of aortic systolic pressure in their series.

In each case an attempt was made to define the nature of the pulmonary stenosis by examining the continuous record of the pressure pulses obtained when the tip of the catheter was withdrawn slowly from the pulmonary artery to the right ventricle (fig. 2). Pressure tracings characteristic of valvular, infundibular and combined valvular and infundibular stenosis have been described by Kirklin and associates.[16] One patient (case 1) appeared to have purely valvular stenosis. Three patients (cases 2, 6 and 7) appeared to have only infundibular stenosis. Three patients (cases 3, 4 and 5) appeared to have combined valvular and infundibular stenosis.

Pulmonary blood flow in each case exceeded systemic blood flow and averaged 6.7 liters per minute per square meter of body surface area (range: 3.9 to 11 liters per minute per square meter), while the systemic flow averaged 3.6 liters per minute per square meter (range: 2.2 to 5.5 liters per minute per square meter). There was a large left-to-right shunt in each case, which averaged 43 per cent of pulmonary flow (range: 25 to 60 per cent). Because of the criteria of selection of these patients, no right-to-left shunt large enough to be detected by measurements of blood oxygen saturation could be demonstrated.

Arterial indicator-dilution curves were recorded in each patient by ear oximeter and simultaneously by a cuvette oximeter through which blood from the radial artery was permitted to flow following injection of T-1824 at various sites in the heart and great vessels. The dilution curves recorded in all patients other than patient 5 had normal appearance times and slopes of increasing dye concentration, indicating that no right-to-left shunt existed in these patients. All of the dilution curves had markedly prolonged slopes of declining dye concentration, indicating left-to-right shunts of considerable magnitude. In case 5, an indicator-dilution curve recorded following injection of dye into the right ventricle had a short appearance time and a small abnormal initial deflection, indicating a right-to-left shunt which amounted to approximately 5 per cent of systemic flow. This shunt was not detectable on the basis of oxygen saturation data.

In two of the patients (cases 2 and 5) the cardiac catheter passed from the right ventricle into the aorta.

Patient 7 differed from the other patients in certain features. There appeared to be a zone of infundibular stenosis which was defined when the cardiac catheter was withdrawn slowly from the pulmonary artery to the right ventricle. The oxygen saturation of the blood in the infundibular area was higher than that in the outflow portion of the right ventricle. For example, the oxygen saturations of intracardiac blood samples, measured in quick succession by the cuvette oximeter on one of several occasions, were: pulmonary artery 85 per cent, infundibular zone 84 per cent, low right ventricle 73 per cent, right atrium 70 per cent. The radial arterial and aortic pressures were 200/45 and 148/57 respectively, when recorded simultaneously. In this case the final diagnosis rested between pulmonary stenosis, ventricular septal defect and aortic insufficiency on the one hand, and rupture of an aneurysm of a sinus of Valsalva with communication between the aorta and the outflow tract of the right ventricle on the other.

Pulmonary Stenosis, Ventricular Septal Defect and Atrial Septal Defect. In addition to pulmonary stenosis and ventricular septal defect, the four patients in group II have an associated defect in the atrial septum (table 3). In each of these four patients there is a left-to-right shunt, but in three of them there is a right-to-left shunt in addition. The findings for each patient are considered below and shown diagrammatically in figures 3 and 4.

Case 1. The catheter crossed an atrial septal defect and passed into the left atrium and left ventricle. Intracardiac pressures of 9/2 and 79/6 were recorded in these positions. Immediately following this the catheter was withdrawn to the right atrium and advanced into the right ventricle, and pressures of 9/4 and 65/5 respectively were obtained at these sites. The patient's hemodynamic status did not appear to have changed between observations. The cardiac catheter did not enter the pulmonary artery, and the diagnosis of pulmonary stenosis depended on the presence of a coarse systolic murmur and thrill at the pulmonary area and x-ray findings of a slight decrease in pulmonary vascular markings

TABLE 3.—*Intracardiac Pressures, Blood Oxygen-Saturation Data, Blood Flow and Shunt Values in Four Cases of Pulmonary Stenosis With Atrial and Ventricular Septal Defects*

Case	Pressure, mm. Hg							% oxygen saturation breathing air			Oxygen radial artery	Arterial oxygen,* physical solution, vols. per 100 cc.	Blood flow index L./min./M²		Shunt	
	Pulmonary artery	RV outflow	Low RV	LV	RA	LA	Radial artery	Mixed venous blood	RV outflow	Radial artery			Pulmonary	Systemic	R-L, % systemic flow	L-R, % pulmonary flow
1†	—	63/6	65/5	79/6	9/4	9/2	100/71	68	74	90	99	0.6	2.5	2.9	25	20
2	12/8	75/6	106/5	—	7/3	—	115/67	70	75	88	97	—	1.7	2.2	35	25
3†	22/13	59/3	66/2	84/3	4/3	11/4	97/62	73	86	96	100	2.2	11.8	6.0	—	50
4†‡	20/12	106/10	93/8	96/6	10/7	11/7	103/67	72	80	84	90	—	5.1	4.8	40	30

* Oxygen content minus oxygen capacity when breathing 99.6 per cent oxygen.

† Patient studied under anesthesia.

‡ Oxygen uptake estimated from tables of normal values.[17]

associated with right ventricular hypertension. The second sound in the pulmonary area, though accentuated, was single.

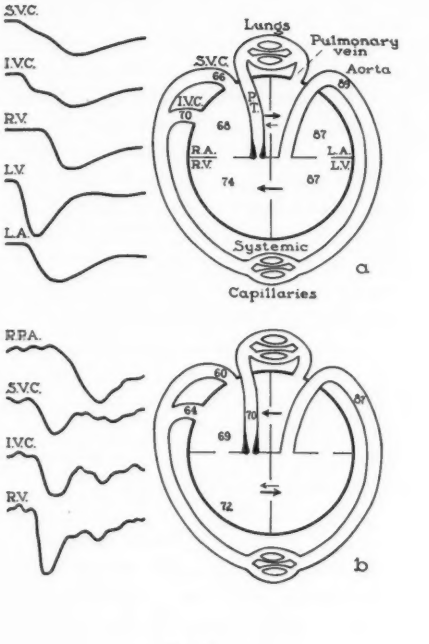
The oxygen saturation of the blood in the right ventricle was higher than that in the right atrium, indicating the presence of an arteriovenous shunt into the right ventricle. While the patient breathed air, the oxygen saturation of the right atrial blood was not higher than that of vena caval blood; but when the patient breathed 100 per cent oxygen, the oxygen saturation of right atrial blood exceeded that of the caval blood by 5 per cent, giving evidence of a left-to-right shunt at atrial level under this circumstance.

An arterial indicator-dilution curve recorded following injection of T-1824 into the right ventricle had a normal appearance time and slope of increasing dye concentration, showing that there was no right-to-left shunt at ventricular level. Dilution curves recorded following injection of dye into the superior and inferior venae cavae had short appearance times and abnormal initial deflections, indicating a right-to-left shunt at atrial level. The initial deflection in the curve recorded following the inferior vena caval injection was larger than that recorded following the superior caval injection. It was estimated that 25 per cent of inferior caval blood and 20 per cent of superior caval blood traversed the defect. The difference in the relative magnitudes of the shunts from each cava, as demonstrated by Swan and co-workers,[14] strongly favors an atrial septal defect as the site of the right-to-left shunt in this instance. These dilution curves are also consistent with a left-to-right shunt of considerable magnitude. A dye-dilution curve recorded following injection of dye into the left ventricle had a normal appearance time and slope of increasing dye concentration for this site of injection. The slope of declining dye concentration was less steep than would be expected from the initial portion of the curve, indicating a left-to-right shunt at or distal to the left ventricle. This dilution curve is compatible with the finding of a higher oxygen saturation in the right ventricle than in the right atrium. The curve recorded following injection into the left atrium is characterized by a more abnormal slope of declining dye concentration and suggests the presence of a left-to-right shunt at atrial level.

Case 2. The left side of the heart was not catheterized in this patient. The blood oxygen saturation in the right atrium was found to be higher than that in the venae cavae and the saturation in the right ventricle was slightly higher than that in the right atrium. This was evidence for the existence of left-to-right shunts at both atrial and ventricular levels.

Spontaneous fluctuations in oxygen saturation were present in this patient and affected the recording of dilution curves of T-1824. When dye was injected into the right pulmonary artery the resultant curve showed a normal appearance time and slowed build-up and disappearance phases. When dye was injected into the venae cavae and right ventricle the resultant curves had short appearance times and abnormal initial deflections, demonstrating the existence of a right-to-left shunt. There was no substantial difference in the initial deflections in the dilution curves recorded following the caval injections, as had been noted in case 1, and these deflections were not larger than the initial deflection in the dilution curve recorded following the right ventricular injection. This demonstrated that a large right-to-left shunt existed at ventricular level and did not support but did not completely exclude the presence of a right-to-left shunt at atrial level.

Case 3. Pressures were measured in all four chambers of the heart. As in case 1, the cardiac catheter passed through an atrial septal defect. The pressures obtained were as follows: right atrium 5/3, left atrium 9/4, right ventricle 66/2 and left ventricle 83/3 mm. of mercury. The blood oxygen saturation was found to be higher in the right atrium than in the venae cavae and higher in the



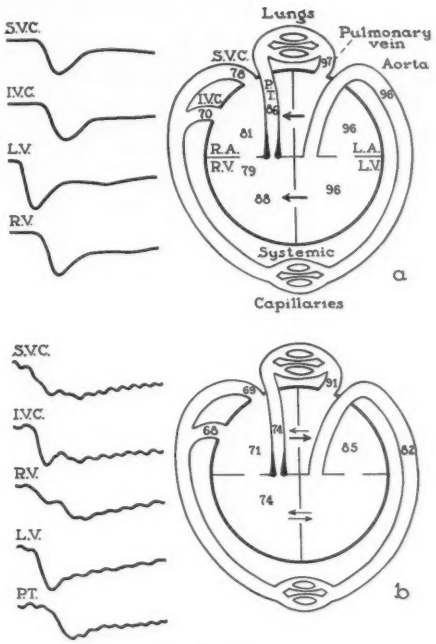


FIG. 3

FIG. 4

FIG. 3 (left) and 4 (right). Representation of the heart and circulatory system for patients in group II. The chambers of the heart are designated: R.A., right atrium; L.A., left atrium; R.V., right ventricle and L.V., left ventricle. The great vessels are designated: S.V.C., superior vena cava; I.V.C., inferior vena cava and P.T., pulmonary trunk. The numerals inscribed in the chambers of the heart or the vessels indicate the per cent oxygen saturation as measured by the cuvette oximeter. The arterial indicator-dilution curves are reproduced to the left of the figure, commencing at the instant of injection of the indicator. The site of injection is inscribed above the beginning of each curve. See the text for a more detailed discussion of the dynamic situation present in each case.

FIG. 3*a* (patient 1). Blood oxygen-saturation data indicated that a right-to-left shunt existed at atrial level and a left-to-right shunt existed at ventricular level. Indicator-dilution curves supported this conclusion and provided evidence of a small left-to-right shunt at atrial level.

FIG. 3*b* (patient 2). Blood oxygen-saturation data showed left-to-right shunts to exist at both atrial and ventricular levels, and indicator-dilution curves demonstrated a large right-to-left shunt at ventricular level.

FIG. 4*a* (patient 3). Blood oxygen-saturation data showed that left-to-right shunts existed at both atrial and ventricular levels. Indicator-dilution curves showed that no right-to-left shunts existed. The indicator-dilution curve recorded following injection of T-1824 into the left ventricle showed that a left-to-right shunt existed at that level.

FIG. 4*b* (patient 4). Blood oxygen-saturation data showed that left-to-right shunts existed at both atrial and ventricular levels. Indicator-dilution curves demonstrated right-to-left shunts at both atrial and ventricular levels and supported the existence of a left-to-right shunt from the left ventricle.

ight ventricle than in the right atrium. This was vidence for left-to-right shunts at both levels.

Indicator-dilution curves recorded following injection of dye into the venae cavae and the right entricle had normal appearance times and normal lopes of increasing dye concentration, showing that here was no right-to-left shunt in this patient. The urves all had prolonged and flattened slopes of declining dye concentration, showing that a large left-to-right shunt existed. A dye-dilution curve was also recorded following injection into the left ventricle. The appearance time and slope of increasing dye concentration were normal, but there was marked prolongation of the slope of decreasing dye concentration, compatible with a large left-to-right shunt from or distal to the left ventricle.

TABLE 4.—*Comparison of Intravascular Systolic Pressures in 26 Normal Subjects,[19] 11 Patients With Tetralogy of Fallot[18] and Seven Patients With Pulmonary Stenosis, Ventricular Septal Defect and Arteriovenous Shunts*

	Pressure, mm. Hg			Right ventricle minus pulmonary artery	Radial artery minus right ventricle
	Right ventricle	Pulmonary artery	Radial artery		
Present series.....	89	31	131	58	42
Tetralogy of Fallot	104	17	118	87	14
Normal subjects*.	27	22	135	5	Not relevant

* Pressures are averaged from series and do not necessarily indicate the exact magnitudes of the gradient of pressure across the pulmonary valve in the normal subjects.

Case 4. Pressures were measured in all four chambers of the heart as in cases 1 and 3. In contrast to the other patients, the hemodynamic status in this patient underwent alteration during the course of study, owing to the occurrence of episodes of nodal rhythm. The pressures in the atria were found to be virtually identical when recorded in quick succession, averaging 10/7 and 13/6 when the rhythm was normal and nodal respectively. The ventricular pressures were also considered to be nearly identical. The oxygen saturation of the blood in the right atrium was slightly higher than that in the venae cavae, and a further increase in oxygen saturation was found in the right ventricle, demonstrating left-to-right shunts at both levels.

Dye-dilution curves recorded following injection of T-1824 into the venae cavae and right ventricle had short appearance times and abnormal initial deflections. The dilution curve recorded following injection of dye into the right ventricle indicated that approximately 20 per cent of the systemic blood was shunted from the right ventricle. The caval curves indicated that approximately 35 per cent of systemic blood was shunted from the venae cavae or sites distal thereto. As in case 1, the initial deflection recorded following the inferior caval injection was larger than that recorded following the superior caval injection. A dilution curve recorded following injection of dye into the left ventricle was similar in contour to that obtained from this injection site in case 1, supporting the evidence for a left-to-right shunt from the left ventricle.

COMMENT

The important determinants of the direction of flow across a ventricular septal defect are the pressure differential between the ventricles and the size of the defect. A major factor controlling right ventricular pressure is the resistance to pulmonary flow. In patients with pulmonary stenosis the main resistance to pulmonary flow is proximal to the lungs, at the stenotic pulmonary valve or in the outflow tract of the right ventricle. Variation in the relative magnitudes of the resistances to pulmonary and systemic blood flow in these patients allows most of the intermediate hemodynamic situations to exist ranging from pure left-to-right shunting, seen in the cases of this report, to predominant right-to-left shunting, as seen in the more classic cases of tetralogy of Fallot.

The basic cardiac malformations in the patients in group I have a certain resemblance to the hearts of patients with tetralogy of Fallot as noted by Moffitt and associates[3] in a group of similar patients. In spite of the anatomic similarity of the congenital anomalies, increased pulmonary blood flow is a feature of the hemodynamic state in these patients, and they may be properly designated as examples of acyanotic congenital heart disease. Comparisons were made between the present group of patients, a series of patients with tetralogy of Fallot[18] and a series of normal subjects[19] studied by cardiac catheterization in this laboratory (table 4). Several interesting features are apparent. In the patients presented in this paper the average pulmonary arterial systolic pressure exceeded that pressure in the patients with tetralogy of Fallot and also in the normal subjects. This suggests that the pulmonary arterial systolic pressure is a function of the pulmonary blood flow. However, comparing the present series of patients with the cases of tetralogy of Fallot, there was a smaller pressure gradient across the pulmonary valve (58 versus 87 mm. Hg) in the presence of a greater pulmonary blood flow (6.7 versus 2.3 L. per minute per square meter). The degree of pulmonary stenosis in the present series of patients must be relatively mild. Barratt-Boyes and Wood[19] have demonstrated a small systolic pressure gradient between the pulmonary artery and the right ventricle in normal subjects.

A considerable pressure gradient existed (average 42 mm. Hg) between the right ventricular systolic pressure and the radial arterial systolic pressure in the present series, whereas there was a much smaller difference between these pressures in the patients with tetralogy of Fallot (average 14 mm. Hg). The radial arterial systolic pressures in the patients with tetralogy of Fallot averaged 114 per cent of the right ventricular systolic pressures. It is interesting to note that Kroeker and Wood[15] found radial arterial systolic pressures to be 112 per cent of aortic systolic pressures in a series of normal subjects.

When the subject of pulmonary stenosis and ventricular septal defect is considered, the relation of the origin of the aorta to the right ventricle is of interest. The aorta was catheterized in two of the seven patients in group I of the present series and in 10 of the 21 cases of tetralogy of Fallot.[18] Chapman and associates[20] considered overriding of the aorta a diagnosis to be made only at necropsy. Gordon and associates[21] believed that overriding of the aorta could be diagnosed if a cardiac catheter passed into the aorta. This conclusion is not necessarily correct. As was shown by Eisenmenger[22] in dog hearts and by Edwards and associates[23] in the human heart, if an artificial defect is made in the membranous portion of the ventricular septum of a normal heart, the aorta communicates directly with both ventricles and a probe or cardiac catheter can be passed from the right ventricle into the aorta.

The four patients in group II were included in this report because they satisfied the basic criteria for selection in that they had pulmonary stenosis, ventricular septal defect and left-to-right shunt. It is felt that anatomically the four patients resembled each other but their circulatory dynamics were quite dissimilar. The nature of the disorder in these four patients is complex and a description of the hemodynamic as well as the anatomic situation is necessary for an adequate assessment of the condition. Any decision about the form of treatment to be used in patients such as these should be based largely on hemodynamic considerations.

Summary

Clinical and hemodynamic data have been presented in 11 cases of pulmonary stenosis and ventricular septal defect with left-to-right shunt. Four of these patients also had interatrial communications and three of these had bidirectional shunts.

The clinical diagnosis depends primarily on the diagnostician's being aware of the possible existence of a left-to-right intracardiac shunt with increased pulmonary blood flow in the presence of signs of pulmonary stenosis. All except one of the first seven patients had a harsh systolic murmur and thrill in the pulmonary area. The pulmonary arterial shadow was increased in all except one of these patients. Other physical signs, the pulmonary vascular markings and the electrocardiograms were more varied.

The technic of selective injections of T-1824, used in conjunction with measurements of blood oxygen saturation in the chambers of the heart and great vessels by cuvette oximeter, was of great value in the definition of the level, direction and magnitude of intracardiac shunts.

Acknowledgment

The authors gratefully acknowledge the critical interest of Drs. H. B. Burchell, J. E. Edwards and E. H. Wood in the preparation of this paper.

Summario in Interlingua

Patientes con stenose pulmonar e defecto ventriculo-septal ha usualmente un dextero-sinistre derivation intracardiac. Le presente reporto offere datos hemodynamic e clinic in re 11 patientes qui ha stenose pulmonar, defecto ventriculo-septal, e sinistro-dextere derivationes. Quatro de iste patientes ha etiam defectos in le septo atrial, e tres ha demonstrabile derivationes ambidirectional. Le nivello e le direction del derivationes esseva determinate super le base de datos de saturation oxygenic del sanguine e de studios de dilution de injectiones indicatori. Le selection del forma de tractamento pro patientes del typo hic discutite debe esser basate in grande mesura super considerationes hemodynamic. Multes resimila patientes con tetralogia de Fallot post succedite valvulotomia pulmonar.

REFERENCES

[1] Deuchar, D. C. and Zak, G. A.: Cardiac catheterization in congenital heart disease—I. Four cases of pulmonary stenosis with increased pulmonary blood flow. Guy's Hosp. Rep. **101:** 1, 1952.

[2] Broadbent, J. C., Wood, E. H. and Burchell, H. B.: Left-to-right intracardiac shunts in the presence of pulmonary stenosis. Proc. Staff Meet., Mayo Clin. **28:** 101, 1953.

[3] Moffitt, G. R., Jr., Zinsser, H. F., Jr., Kuo, P. T., Johnson, Julian and Schnabel, T. G., Jr.: Pulmonary stenosis with left to right intracardiac shunts. Am. J. Med. **16:** 521, 1954.

[4] Cournand, Andre and Ranges, H. A.: Catheterization of the right auricle in man. Proc. Soc. Exper. Biol. & Med. **46:** 462, 1941.

[5] Wood, E. H., Geraci, J. E., Pollack, A. A., Groom, Dale, Taylor, B. E., Pender, J. W. and Pugh, D. G.: General and special technics in cardiac catheterization. Proc. Staff Meet., Mayo Clin. **23:** 494, 1948.

[6] Burchell, H. B. and Wood, E. H.: Remarks on the technic and diagnostic applications of cardiac catheterization. Proc. Staff Meet., Mayo Clin. **25:** 41, 1950.

[7] Wood, E. H.: Special technics of value in the cardiac catheterization laboratory. Proc. Staff Meet., Mayo Clin. **28:** 58, 1953.

[8] Callahan, J. A., Brandenburg, R. O. and Swan, H. J. C.: Pulmonary stenosis and interatrial communication with cyanosis: Hemodynamic and clinical study of 10 patients. Am. J. Med. **19:** 189, 1955.

[9] Nicholson, J. W., III, Burchell, H. B. and Wood, E. H.: A method for the continuous recording of Evans blue dye curves in arterial blood, and its application to the diagnosis of cardiovascular abnormalities. J. Lab. & Clin. Med. **37:** 353, 1951.

[10] Swan, H. J. C., Zapata-Diaz, J. and Wood, E. H.: Dye dilution curves in cyanotic congenital heart disease. Circulation **8:** 70, 1953.

[11] Broadbent, J. C. and Wood, E. H.: Indicator-dilution curves in acyanotic congenital heart disease. Circulation **9:** 890, 1954.

[12] Swan, H. J. C. and Wood, E. H.: Localization of cardiac defects by dye-dilution curves recorded after injection of T-1824 at multiple sites in the heart and great vessels during cardiac catheterization. Proc. Staff Meet., Mayo Clin. **28:** 95, 1953.

[13] Wood, E. H.: Normal oxygen saturation of arterial blood during inhalation of air and oxygen. J. Appl. Physiol. **1:** 567, 1949.

[14] Swan, H. J. C., Burchell, H. B. and Wood, E. H.: The presence of venoarterial shunts in patients with interatrial communications. Circulation **10:** 705, 1954.

[15] Kroeker, E. J. and Wood, E. H.: Comparison of central and peripheral arterial pressure pulses in man. Abstracts of Communications. XIX International Physiological Congress, Montreal, 1953, vol. 1, p. 535.

[16] Kirklin, J. W., Connolly, D. C., Ellis, F. H., Jr., Burchell, H. B., Edwards, J. E., and Wood, E. H.: Problems in the diagnosis and surgical treatment of pulmonic stenosis with intact ventricular septum. Circulation **8:** 849, 1953.

[17] Du Bois, E. F.: Basal Metabolism in Health and Disease. Ed. 2, Philadelphia, Lea & Febiger, 1927.

[18] Callahan, J. A.: Pulmonary Stenosis and Associated Intracardiac Shunts; a Clinical and Hemodynamic Study of 55 Patients. Thesis, Graduate School, University of Minnesota, 1955.

[19] Barratt-Boyes, B. G., and Wood, E. H.: Unpublished data.

[20] Chapman, D. W., Earle, D. M., Gugle, L. J., Huggins, R. A., and Zimdahl, Walter: Intravenous catheterization of the heart in suspected congenital heart disease: Report of seventy-two cases. Arch. Int. Med. **84:** 640, 1949.

[21] Gordon, A. J., Lasser, R. P., Moscovitz, H. L., Brahms, S. A., and King, F. H.: The diagnosis of overriding aorta: With special reference to circulation time tests. Am. J. Med. **15:** 158, 1953.

[22] Eisenmenger, V.: Ursprung der Aorta aus beiden Ventrikeln beim Defect des Septum ventriculorum. Wien. klin. Wchnschr. **11:** 25, 1898.

[23] Edwards, J. E., Dry, T. J., Parker, R. L., Burchell, H. B., Wood, E. H. and Bulbulian, A. H.: An Atlas of Congenital Anomalies of the Heart and Great Vessels. Springfield, Charles C Thomas, 1954.

Studies Made by Simulating Systole at Necropsy

VII. Clinical Methods for Estimating the Work of the Left Ventricle.

With a Note on the Diminution of Heart Work as Age Advances

By ISAAC STARR, M.D., S. I. ASKOVITZ, M.D., W. FEDER, M.D. AND A. SCHILD, PH.D.

"Left ventricular" work can be estimated with great accuracy in cadaver experiments in which both pressure curves and curves of cardiac output at each instant of systole were recorded. Using these accurate estimates as a target, methods have been sought which would permit the estimation of cardiac work from measurements which could be made in the clinic and the accuracy of such methods has been assessed. A method of approximating the left ventricular work has been devised which is so simple that it could be used by any doctor practicing medicine.

THERE can scarcely be any doubt that knowledge of the heart's work is the most important single aspect of any quantitative assessment of cardiac function and that if one could estimate heart work with reasonable accuracy, it would lead to a better understanding of heart disease. Cardiac output is of importance because it is the concern of the rest of the body, but noncardiac factors, such as changes in vascular resistance, greatly influence the relation of cardiac work to output. The senior author's interest in this problem has extended for many years[1]; indeed, his long concern with cardiac output methods has stemmed largely from the fact that such results would permit rough estimations of cardiac work.

Most textbooks of physiology discuss the heart's work,[2] but this aspect of cardiac performance has received little attention in the clinical literature, doubtless because methods of estimating it, well suited to the clinic, have not been available. This study aims to provide such methods.

From the Department of Therapeutic Research of the Medical School of the University of Pennsylvania, Philadelphia, Pa.

This work was supported by research grant 625 C (1 to 5) from the National Heart Institute of the National Institutes of Health, United States Public Health Service.

Indeed, the formula most frequently employed by physiologists for estimating cardiac work gives only an approximation of the true value. It is as follows:

$$Work = QR + \frac{Mv^2}{2g} \qquad \text{(a)}$$

Where Q = volume of blood expelled from the heart per beat, R = resistance, usually expressed as mean blood pressure in mm. Hg $\times$ 13.6, v = velocity of blood at the root of the aorta, M = mass of blood, and g = acceleration due to gravity. The second term on the right side of equation (a) represents the work done in imparting velocity to the blood, and M is usually taken as the cardiac output in cc. times the specific gravity of blood. In resting subjects this term represents so small an amount of the total cardiac work performed that it is usually neglected. In our old studies,[1] it seldom exceeded 2 per cent of total work. Additional terms have been suggested for cardiac work equations,[3] but of small magnitude and often difficult or impossible to estimate, these have been usually neglected also.

It has long been realized that the calculation of work from cardiac output and mean blood pressure by formula (a) might involve large errors. The main error is involved in the assumption that the output and pressure can

be multiplied together without regard to time. To secure a correct estimate of work, the flow at every instant must be multiplied by the resistance at that instant, and the curve of cardiac ejection, instant by instant, has seldom been recorded. In hearts with a single ventricle, such as in the frog and turtle, the measurement has been made. Many years ago Otto Frank[3] obtained such curves for the isolated frog heart and estimated work by this means. Later Katz[4] secured similar curves by enclosing the isolated turtle heart in a volume recorder, and he also estimated work. But similar estimates of work are much more difficult to secure from mammalian hearts beating in situ, for volume recorders then contain both ventricles and so record the sum of the outputs of both at each instant, and this value cannot be used with the pressure in either pulmonary artery or aorta at the same instant, in a calculation of work, without introducing errors which might be large.

In a series of experiments performed on fresh cadavers in this laboratory by Starr, Schnabel and Mayock,[5, 6] systole was simulated at necropsy. From two of the records obtained, the cardiac ejection curve and central blood pressure, it was possible to estimate the work of each "systole" as work was defined by Newton, by multiplying pressure and the differential of volume instant by instant and taking the integral of the result, a method which we have no hesitation in claiming to be far more accurate than any which can be applied to living man or mammals. Also, the same two curves gave us data from which work could be estimated in the usual way, by formula (a).

The remaining two curves of our records, peripheral blood pressure and the ballistocardiogram, provided measurements of a type which could be made on any patient in the clinic. Therefore, with the accurate values of work estimated from the first two curves as a target, we have sought the best means of estimating left ventricular work from measurements that could be made by doctors working in the clinic. The mathematical analysis of the data required for this purpose was undertaken by the three younger collaborators of this paper who were well fitted both by training and inclination to carry out this difficult and exacting task. Dr. Askovitz acted as advisor and coordinator of this part of our work.

The principle underlying the mathematics which will determine the best method, defined as that method in which the sum of the squares of the errors is at a minimum, has long been known; and such computations, formerly of only limited value to medical investigators because they were so laborious to carry out, have become an important tool in medical research since the development of the electric computing machines. Thus, although the details of our mathematical methods may not be understood by many doctors, both the aim and the result can be readily comprehended by everyone. We aimed to produce a clinical method of estimating the work of the heart, a method of reasonable accuracy and of such simplicity that it could be used by any doctor practicing medicine, and we believe that we have come close to this goal.

Finally, after devising a simple method for estimating left ventricular work from blood pressure, we have estimated such work from published data on the average blood pressure of large groups of the population, and so determined the changes in the average heart work of healthy persons as age advances. The results show clearly that, as age advances, the average work performed by the heart at each beat diminishes markedly, and at the age of 60 the average cardiac stroke work is about two-third of that at 20 years.

Material and Methods

The physical characteristics and necropsy findings of the cadavers used have already been reported[5, 6, 7] and the method of simulating systole has been described in detail.[5, 6] The experiments themselves were performed by Starr, Schnabel and Mayock. In brief, large cannulas were placed in the aorta and pulmonary artery and, after a diastolic pressure had been imparted by perfusion into a femoral artery, systole was simulated by injecting into these large arteries from syringes, the position of the pistons of these syringes being recorded continuously by an optical system. The record

consisted of four curves recorded simultaneously; the cardiac ejection curve, curves of blood pressure in the aortic arch and femoral artery, and the ballistocardiogram. These records were carefully tested for alignment. Examples have been illustrated in previous publications.[5, 6]

Such records were obtained from two groups of experiments, those in which the cadavers were perfused with blood and those in which they were perfused with water. The former group comprised 53 "systoles" in six cadavers. These experiments most closely reproduced conditions occurring during life and they were performed at the end of our long series, after our technique had been brought to its highest point. Therefore, in this presentation, the chief emphasis will be placed on the data secured from these experiments, although we shall also refer to results secured on a sample of 63 "systoles" secured in six cadavers perfused with water. The physical characteristics and the necropsy findings in this latter group have also been published.[7] One subject, P. L., occurs in both groups having been perfused with water in some "systoles", with blood in others.

Cardiac Work Estimates: Before designing our attack on the work of the heart, we had a philosophical problem to consider, for we must define our target. We must ask ourselves what the heart's work consists of, and how this was to be expressed to yield values of the greatest usefulness. We do not regard this question as closed.

The senior author has long been interested in the problem of the mathematic expression of muscular work[8] and he believes that there are many advantages in expressing it as the integral of the product of mass and acceleration, the latter measured with the acceleration due to gravity as base line. Cardiac work could be expressed this way also. However, the chief advantage of the newer system is that static and dynamic work are measured in similar terms, and the heart's work is altogether dynamic as the pressure load during diastole is taken off the heart muscle by the valves. So the advantage of the new system, as an expression of cardiac work, would be problematic, and also, in order to apply it, our cardiac ejection curves would have to be differentiated a second time and this would markedly increase the error of the estimate. For these reasons, we have contented ourselves with the classic Newtonian method of expressing cardiac work in this paper, and we will use those values as our target.

The task of estimating Newtonian work by integration of the 53 curves secured on "systoles" produced by injections of blood, was undertaken by Dr. Feder. As a first step in these estimates, the "cardiac" ejection and aortic pressure curves were enlarged by means of a pantograph and then measured. From these measurements, work was estimated, the theory underlying the procedure being as follows:

The concept of work done by a force in displacing a body is a basic one in the study of dynamics, and is generally defined as the product of the displacement undergone by the body, times the component of the force in the direction of the displacement. Whenever force and displacement have the same direction in common, then work equals simply force times displacement. Now it is shown in practically all texts of calculus or physics that in the case of a rigid piston and cylinder arrangement, the total work can be expressed in terms of pressure (P) and volume (V) changes by means of the formula $W = \int P\,dV$, or if P and V can both be expressed in terms of time (t), then:

$$W = \int P \frac{dV}{dt}\,dt \qquad \text{(b)}$$

In the cadaver experiments, the values of P and V were recorded graphically in terms of time, and were therefore available for the evaluation of the integral (*b*). However, it must be remembered that the formula is true strictly for a rigid tube only, and also does not take into account changes in kinetic energy. Nevertheless, the integral does represent by far the major portion of the effective cardiac work.

The problem of determining the numerical value for the integral from the graphical data was approached in several ways. The first technic involved estimating $\frac{dV}{dt}$ from the graph of V, then tabulating corresponding values of P and $\frac{dV}{dt}$. The values of $P\frac{dV}{dt}$ were next calculated, and a new graph prepared charting $P\frac{dV}{dt}$ against time. The area under the curve, as measured by a planimeter, gives the desired integral. It might be remarked at this point

that the pressure here is an absolute value, and that attention must be paid to using the proper units.

A second method, depending upon the composite plotting of P and V on the same graph, was then tried. This graphic representation of cardiac work was described by Straub,[10] although it does not appear to have been employed for numerical calculations. The details of our method of estimating work by this means are set forth in figure 1 and its legend. For any particular value of time t, the x- and y-coordinates of a point E on the composite P-V graph are equal to $x_E = BD = V(t)$ and $Y_E = AC = P(t)$,

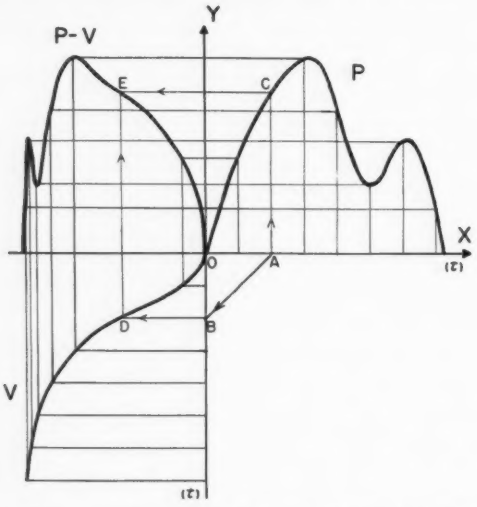


FIG. 1. An illustration of the graphic method used for estimating cardiac work by evaluating $\int Pdv$ from the recorded pressure-time and volume-time curves.

After making four quadrants by drawing X and Y axes, one proceeds as follows:

(1) Reproduce the recorded pressure-time curve in the upper right-hand quadrant, to any convenient scale, with time plotted toward the right and increasing pressures upward. The heavy line in the right upper quadrant is the reproduction of such a curve.

(2) Transcribe the recorded volume-time curve into the lower left-hand quadrant, to any convenient scale, with time plotted downward and increasing volumes toward the left; this reversal of the usual orientation is best achieved by tracing from the reverse side of the original volume-time curve, with thin tracing paper and illumination from below. The heavy line in the left lower quadrant is the reproduction of such a curve.

(3) After choosing suitable intervals of time, mark them as a series of points on the time-axis (OX) of the pressure-time curve, and mark corresponding points on the time-axis of the volume-time curve, (e.g. B corresponds with A in time).

so that Work = $\int P\,dV = \int y\,dx$ = Area under or surrounded by the P-V curve. Although less direct than the first method, the P-V diagram technique proved to be considerably easier to carry through, and it was therefore used exclusively for all the final calculations.

The integrations thus calculated by Dr. Feder compute with exactitude the work performed in raising the pressure. That performed in imparting velocity to the blood, represented by the second term of the right side of equation (a), $\frac{Mv^2}{2g}$, was calculated by Dr. Schild for each of these experiments. Knowledge of the internal diameter of the tip of the glass aortic cannula permitted him to estimate linear velocity at the orifice. M, the mass moved, is usually estimated from the stroke volume and the specific gravity of blood. When the estimates were made in this way, it became obvious that the work thus represented was negligible in our experiments, being always less than 2 per cent of the total. But we believe that M, the mass moved at any instant, is in all probability much larger than the stroke volume, as blood is pushed on ahead of that issuing from the heart during ejection. We see no simple way of determining this quantity and so we have not attempted to correct the usual estimate of the velocity component of cardiac work, which we believe to be too small. But we see no reason to doubt that the first term of the right side of equation (a) represents the great bulk of the heart's work. Indeed, in the first part of the statistical analysis, Dr. Schild compared the results secured by both the inclusion and omission of the velocity component and found no material difference in the correlation; so we have

(4) For each time point on the X axis (e.g., A on the diagram), draw a vertical line upward to the pressure curve (AC); from each of the corresponding time points on the Y axis (e.g., B on the diagram) draw a horizontal line to the left to the volume-curve (BD).

(5) From each point of the intersection with the pressure curve, (e.g., at C) draw a horizontal line to the left, and from the corresponding point of intersection with the volume curve, (e.g., at D) draw a vertical line upward. Extend each of these lines until they meet (e.g., CE and DE at E).

(6) Repeat this process for the entire series of time-values, and sketch a smooth curve through the points of intersection so obtained, in the upper left-hand quadrant; this derived curve is shown as the heavy line in the left upper quadrant.

(7) Estimate the magnitude of the area under this "pressure-volume" curve by any suitable method (counting squares, mechanical planimeter, linear map-measure, integration formulas, or direct graphic methods).[9] This area represents the integral, $\int Pdv$, and so it is the measure of work.

TABLE 1.—*"Left Ventricular" Work calculated as Pdv from Continuous Aortic Arch Blood Pressure and Cardiac Ejection Curves during the Simulation of Systole in Cadavers Perfused with Blood*

Subject and "Systole" No.	Gm.M. Work	Subject and "Systole" No.	Gm.M. Work	Subject and "Systole" No.	Gm.M. Work	Subject and "Systole" No.	Gm.M. Work
R.R. 1	49.6	H.Z. 1	66.2	J.W. 6	39.9	M.L. 1	68.3
2	40.5	3	69.5	7	40.9	2	47.9
3	32.9	4	60.0	8	37.8	3	75.0
4	42.3	5	148.6	9	33.1	4	84.3
5	91.9	6	108.8	10	56.6	5	22.4
6	65.0	7	44.4	11	46.3	6	13.1
7	88.3	8	117.2	12	48.8	8	41.5
8	87.8	9	67.7	14	61.7	9	66.4
9	49.5	10	157.8	15	13.9		
10	108.7	11	27.6			P.L. 3	68.8
				M.M. 4	56.3	4	71.3
11	30.2	13	31.8	5	62.3	5	193.9
12	32.7			6	46.3	6	107.9
13	22.7			7	54.9	7	33.1
14	36.8			8	88.8		
15	52.7						

neglected this part of the heart's work in the results to be reported here.

Cardiac work was thus estimated by integration of the curves secured in 53 simulated systoles performed in six cadavers, in all of which blood had been used as perfusion fluid. These results are given in table 1. These data may be compared with measurements of the blood pressures and ballistocardiograms secured in the same experiments, which have been published previously.[5, 6] One omission deserves comment. Work was not estimated by Dr. Feder from the curves of the second systole of subject H. Z. through an oversight. The record of this "systole", mounted to provide an illustration for a previous publication, had been stored in a different place and its absence was not noticed until the statistical analyses had been largely completed. There seemed no reason to undertake the extra labor which would have been required to insert this item into the data at that time. When work is calculated approximately by formula (a), the relations found in H. Z. 2 are similar to those of the rest of the data.

Before turning the data over to Dr. Schild for statistical analysis, the question of omitting those secured in certain less perfect experiments was raised. In a previous study of methods of estimating stroke volume from blood pressure, the statistical analysis was performed twice, both with and without the inclusion of data from several less perfect experiments and the results secured by the latter method were preferred. In this analysis of data pertaining to work, we have been somewhat more rigid and we have not omitted any results except for most obvious reasons, such as the following. Of the experiments in which blood was used as perfusing fluid, we could not use three experiments, those in which curves of pulmonary artery pressures were secured, because no record of central blood pressure was taken. We also thought it wise to omit "systoles" 10 and 11 in J. W. and 5 in M. M. because the durations of "systole" so far exceeded that ever found during life, their theoretical pulse rates being 20 per minute or less. The five "systoles" secured in P. L. provided good blood pressure data, but the ballistocardiograms were imperfect—all of them lacked an I wave—so these data were used only in relating work to the blood pressure alone. After these omissions, there remained 50 "systoles" from which work could be related to blood pressure alone and 45 from which work could be related to the ballistocardiograms, all coming from experiments in which blood was used as perfusion fluid. From these data, our chief conclusions will be drawn.

In the experiments in which cadavers were perfused with water we also had a wealth of other data against which these conclusions could be tested. The technical deficiencies of these "water" experiments have been described in detail.[7] Theoretically, differences in viscosity between water and blood would result in different pressure-flow relationships. When water was used, aortic pressure fell so rapidly after perfusion stopped that, to secure normal diastolic pressures at the onset of "systole", we were forced to continue the femoral perfusion during systole; so the amount of fluid entering the aorta during systole exceeded that measured in the syringes. This error was certainly negligible when low aortic pressures were sought, but of larger magnitude when, to secure hypertension, we had to force water into the femoral artery under pressure. When blood was used, pressure was so much better maintained after perfusion was stopped, that we had no difficulty securing normal or hypertensive diastolic pressures at the onset of systole, although femoral inflow was always terminated just before "systole".

Also, in these water experiments the technic of securing good records of blood pressure was mastered before that of regularly securing perfect ballistocardiograms, and these records were unsatisfactory in many of the early experiments.

For these reasons it did not seem worthwhile to undertake the labor of estimating true work by integration in these "water" experiments, but work could be readily approximated from the stroke volume measured in the syringes and the pressure in the root of the aorta by means of formula (*a*) without the velocity component. So, despite their technical differences it seemed well worth while to compare the data secured in the water experiments with the conclusions drawn from the blood experiments in so far as the relation of work to peripheral blood pressure was concerned.

The sample chosen for this study from the data of subjects perfused with water differed somewhat from that used in a previous study.[7] In the present study the results secured in E. L. were omitted because, in this experiment alone, the carotid arteries were tied off, a difference of technic which might be expected to change the pressure-flow relationships, although in fact, the great majority of the values found conform with the rest of our data. In the former study, we rejected data from several "systoles" conducted in high hypertension both because of the technical difficulty mentioned above, and with the thought that the resulting pulse pressures were so large, or the blood pressure so high that such values were not to be expected during life; in the present sample no data have been rejected for such reasons. So, except for the omission of data secured in 2 systoles which could not be checked because a photograph, originally faint, faded out with the passage of time, all the 63 samples of our last series are consecutive, which is of itself ample demonstration that the technique of recording blood pressures had been mastered.

Finally, we must discuss the method of estimating the mean blood pressures used in our calculations of work made without integration. Our first inclination was to estimate mean blood pressure by the simplest possible method as follows:

$$\textit{Mean pressure} = \frac{(\textit{systolic pressure} + \textit{diastolic pressure})}{2} \quad \text{(c)}$$

diastolic pressure being taken as the low point of pressure existing just before the onset of systole and systolic pressure as the highest point attained by the pressure curve during systole. When mean pressure is thus estimated the value exceeds the mean of the integral of the aortic pressure curve. But in estimating the heart's work, one is not concerned with aortic blood pressures existing during diastole, but only with those existing during ejection. The mean pressure of that part of the pressure curve to which the contracting heart is exposed is certainly higher than the mean of the whole pressure curve to which the arteries are exposed. Therefore, we tried another simple formula believed to yield a result closer to the mean value of the changing pressure of the systolic portion of the pressure curve, as follows:

$$\textit{Mean pressure} = \frac{(2\ \textit{systolic pressure} + \textit{diastolic pressure})}{3} \quad \text{(d)}$$

However, when we used this formula we found no improvement in the regressions which measured our ability to estimate work, so we returned to the use of formula (*c*) because of its slightly greater simplicity.

Results and Discussion

All our results deal with what has been called the external or effective work of the left ventricle, and this has been estimated from our data in many ways. For convenience of expression, we propose to designate as "*true*" *work* the values secured by integration, while the values estimated without integration, from the product of stroke volume measured in the syringes and mean central blood pressure, will be called *approximate work*. The results secured from estimations made from ballistocardiograms and peripheral blood pressure, or from peripheral blood pressure alone, that is, from data of a type readily available to clinicians, will be called *clinical estimates of work*. We shall concern ourselves solely with work per beat in this paper.

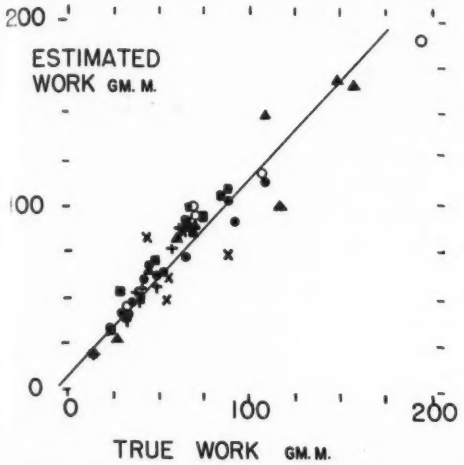


FIG. 2. Tests of the simple method of estimating work most commonly used by physiologists. The estimate (vertical axis) is made from the product of stroke volume, measured in the syringes, and mean blood pressure, taken in the root of the aorta. The points shown represent data secured on 6 subjects perfused with *blood*. Data secured on the different subjects are represented as follows: squares, M. L.; triangles, H. Z.; circles, P. L.; dots, R. R.; crosses, J. W.; x's M. M.; The solid line is the calculated best line corresponding with regression no. 76 of table 2. The correlation coefficient between the estimate and true work is 0.95.

pressures were 237/119 and 233/132, the two smallest 68/31 and 90/20 mm. Hg; the two highest theoretic pulse rates were 400 and 207; the two smallest, 25 and 40 per minute; so the values covered a wide range in these experiments also.

Tests of the approximation formula: Work = QR

Our first step was to determine the accuracy of the approximation usually used in the estimation of the heart's work. Approximate work can be calculated both from blood pressure taken at the root of the aorta and from peripheral blood pressure. The dot diagram relating true work to the approximation calculated from stroke volume and *central* blood pressure is given as figure 2 and this regression equation is given as equation 76 of table 2.* From these results it is evident that work calculated from formula (a) either with or without the second term is, indeed, only an approximation of true work, but it is a good approximation. Katz,[4] in experiments on isolated turtle hearts, also found the error of a similar approximation of cardiac work to be large, averaging −7 per cent and ranging from +123 per cent to −37.8 per cent. Frank,[3]

TABLE 2.—*Regression Equations Relating "True" Left Ventricular Work Determined by Integrating the Flow and Pressure Curves with Estimates Made from Stroke Volume Measured in the Cadaver Experiments Multiplied by Mean Central or Peripheral Blood Pressure*

Equation No.	Equations	σ Gm.M.
76	True Work (*Gm.M.*) = −8.83 + 0.93 (Stroke volume *cc.*) (mean aortic B.P. *mm.Hg*)(13.6) (10^{-3})	10.9
77	True Work (*Gm.M.*) = −6.37 + 0.89 (Stroke volume *cc.*) (mean femoral B. P. *mm. Hg*)(13.6) (10^{-3})	12.0

In the 50 "systoles" produced by injections of blood, the true work ranged from 13.1 to 193.9 Gm.M. which covers the range to be expected in clinical conditions and provides a diversity of values ideal for testing the accuracy of the simple methods we planned to devise. The diversity of blood pressures and theoretic pulse rates was also large in these experiments, as has been reported.[5, 6] In the sample of 63 systoles produced by injections of water, the approximate work ranged from 12.6 to 150.6 Gm.M., the two largest blood from data on isolated frogs hearts, estimated this error to average 10 per cent. In our data,

* The regression equations of this paper have been numbered serially with those of a previous communication[7] derived from the same body of data. Other equations mentioned in this paper have been given letters. The factor concerned with the weight of mercury (13.6) and that needed to correct the decimal point to give the desired units (often 10^{-3}) have been left as separate items in most of the equations because we thought this would enable more readers to see how the regression lines given in the figures were related to the regression equations of the tables.

in one-third of the tests, the error exceeds 10.9 Gm.M. which is 15 per cent of the average resting healthy young adult value secured by a method to be described.

The scatter inherent in the approximation method of formula (a) is of great interest because it represents the limit of excellence possible for a really simple clinical method. It is true that catheters can be passed to the arch of the aorta in man and that the contour of the cardiac ejection curve can be estimated with reasonable accuracy by an adjusted integration of the curves of blood pressure recorded there, in the manner described in a previous communication.[11] Therefore, means are at hand by which left ventricular work could be estimated in the clinic by integration. But the practical difficulties of such an estimation are so obvious that we were encouraged to search for methods requiring neither integration nor catheterization. In such a method, we cannot expect a standard deviation of less than 16 per cent of the mean young adult value and we can only hope to approach that value as closely as possible.

Our ability to estimate true work from stroke volume and *peripheral* blood pressure is given by the regression equation 77 in table 2. From the scatter about this regression, one can estimate the error entailed by computing cardiac work from estimations of stroke volume made in the clinic, and peripheral blood pressure, under the most unlikely circumstance that the cardiac output method employed had an accuracy equal to our ability to measure the output by reading a 100 cc. syringe before and after ejection. In two-thirds of the estimates, the error would be less than 18 per cent of the resting healthy young adult mean. The loss of accuracy, resulting from employing peripheral rather than central pressures, is not great and we were encouraged to seek for simple methods depending on peripheral measurements.

Estimations of Work from Ballistocardiograms and Peripheral Blood Pressure.

Since there is increasing evidence[12] that stroke volume can be measured by ballistocardiograms of the type we employ under

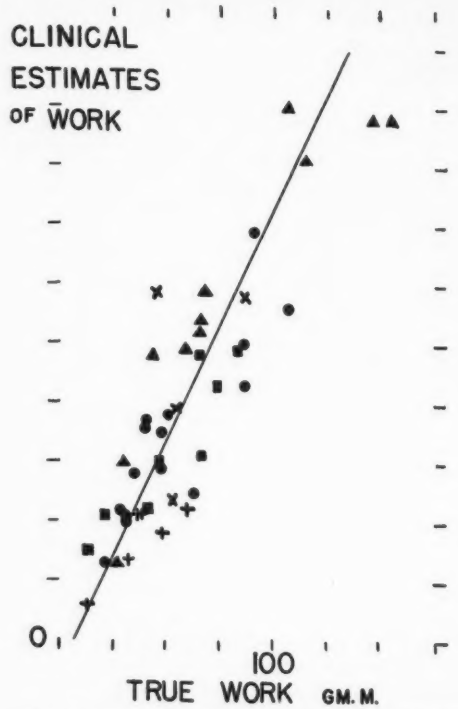


FIG. 3. Tests of clinical work estimates made from ballistocardiograms. The estimates were made from the square root of the amplitude of the I and J waves, mean peripheral blood pressure obtained by puncture of the femoral artery, and the subjects' weight. The estimates are recorded in arbitary units. Data from 6 subjects perfused with *blood*. Symbols as in figure 2. The best line shown corresponds with regression equation no. 82 of table 3. The correlation coefficient of the estimates with true work is 0.88.

many conditions, though not in all, it seemed proper to discover whether true left ventricular work could be estimated from ballistocardiograms and mean blood pressure in our cadaver experiments. Accordingly, we first used the formula suggested by Tanner[13] for estimating stroke volume from ballistocardiograms, multiplied the result by mean peripheral blood pressure and compared the resulting clinical estimate of work with true work. The correlation, $r = 0.82$, is good, but work is seriously overestimated, because the Tanner formula overestimates stroke volume.[12] As it has also been found that the inclusion of a factor for body size improves the estimation of cardiac

output, the effect of using the subject's weight and surface area in estimating work was also studied. Finally, without making an attempt to employ a stroke volume formula, we simply studied the correlation between true work and the product of mean blood pressure and the square root of the altitudes or areas of the ballistic I and J waves, with and without the inclusion of factors related to the subject's size. One of these dot diagrams is reproduced as figure 3. The regression equations are given in table 3. In computing these equations, the ballistocardiogram measurements used have been adjusted to a calibration such that 280 Gm. displaced the light spot 1 cm. on the record.

From these results, it is evident that the correlation of such estimates and true work is extremely strong, for their correlation coefficients range from 0.82 to 0.88, values far exceeding 0.29, the level of significance for $p = 0.05$. The inclusion of an item related to body size gives a slightly better estimate of work. But the scatter about each of the three regressions employing Tanner's formula with and without the size factor, equations 78, 79 and 80 in table 3, is not significantly different. Estimates made directly from measurements of the ballistocardiogram without attempting to measure stroke volume are a little better than when the stroke volume formula is employed. But once more the standard deviations about the regressions 81, 82, 83 and 84 in table 3 are not significantly different. So we have not demonstrated to our satisfaction that one of these methods is better than another.

An interesting theoretic point must be discussed here. Should one expect to measure Newtonian work by multiplying blood pressure by the amplitude of the ballistocardiogram, the latter being a force measurement? Newtonian work is related to velocity, force to acceleration. The product of ballistic amplitude and blood pressure would be more closely related to work defined as the product of mass and acceleration, integrated with respect to time.[8] But in all probability the two kinds of work would be closely correlated under most physiologic and clinical conditions, so it should occasion no surprise that the product of ballistic amplitude and blood pressure is found strongly correlated with Newtonian work.

Certainly, left ventricular work can be roughly estimated from the ballistocardiogram and blood pressure in these experiments and one has every reason to expect that such work could be estimated with equal accuracy in the great majority of patients. But, as in most simple methods, one must envision certain limitations. In the cadaver experiments which provided the results used to make these regressions, the injections into the aorta and pulmonary artery were kept similar. But the forces producing ballistocardiograms secured during life are derived from both sides of the heart and the relation between right and left

TABLE 3.—*Regression Equations Relating "True" Left Ventricular Work with Estimates Made from Peripheral Blood Pressure and Various Aspects of the Ballistocardiogram; Some Including Factors Related to the Size of the Subjects*

Equation No.	Equations	σ Gm.M.
	Let x_1 = Tanner's stroke volume formula = $100\sqrt{[2\text{ (I wave area } mm.\ sec.) + \text{(J wave area } mm.\ sec.)]}\sqrt{\text{cycle } sec.}$	
78	True work $Gm.M. = -3.91 + (0.68\ x_1)$ (mean femoral B.P. $mm.Hg$)(13.6)(10^{-3})	17.9
79	True work $Gm.M. = 5.43 + (1.26\ x_1)$ (mean femoral B.P. $mm.Hg$) (wt. kilo) (10^{-4})	17.1
80	True work $Gm.M. = -1.15 + (0.53\ x_1)$ (mean femoral B.P. $mm.Hg$)(surface area $sq.m.$) (10^{-2})	16.2
	Let $x_2 = \sqrt{\text{altitude of I + J waves } mm.}$	
81	True work $Gm.M. = 3.35 + (1.81\ x_2)$ (mean femoral B.P. $mm.\ Hg$) (10^{-1})	17.3
82	True work $Gm.M. = 7.96 + (0.27\ x_2)$ (mean femoral B. P. $mm.\ Hg$) (weight $Kg.$) (10^{-2})	15.1
83	True work $Gm.M. = 5.12 + (1.06\ x_2)$ (mean femoral B. P. $mm.\ Hg$) (surface area M^2.) (10^{-1})	15.1
	Let $x_3 = \sqrt{\text{area of I + J waves } (mm.\ sec.)}$	
84	True work $Gm.M. = -0.75 + (0.54\ x_3)$ (mean femoral B. P. $mm.Hg$) (surface area M^2.)	16.0
	Mean of true work estimates = 59.39. σ, the scatter about this mean =	32

ventricular output varies with the respiratory cycle; so an average would have to be used in conjunction with average arterial blood pressure to yield an estimate of work comparable with that of the experiments cited above. Of more moment is the fact that in certain severe clinical situations, the normal relation between the right and left ventricular forces might well be upset leading to a distorted ballistocardiogram which, when used in conjunction with arterial blood pressure, could not be expected to provide a good estimate of left ventricular work. These disadvantages would disappear in an estimate of work made from arterial blood pressure alone, so we turned our attention to the development of such a method.

Estimations of Left Ventricular Work from Peripheral Blood Pressure Obtained by Arterial Puncture.

In a previous communication,[7] a series of formulae relating blood pressure to stroke volume were set forth. Of these, formula No. 59 relating stroke volume to peripheral pulse pressure, diastolic pressure and age seemed best adapted to our purpose. Accordingly, the stroke volume was estimated by this formula from data secured in each systole of the group perfused with blood and the result multiplied by the corresponding mean peripheral blood pressure to provide a clinical estimate of work which could be compared with true work. The dot diagram showing the relationship is reproduced as figure 4 and the regression equation is given as No. 85 in table 4. The standard deviation about the regression is 14.9 Gm.M. or 22 per cent of the mean value for left ventricular work in healthy young adults, so that in two-thirds of the estimates the error is less than this amount. Obviously, this clinical method of estimating work is a rough one. However, it must be recalled that a large part of this scatter, a standard deviation of 10.8 Gm.M., is to be attributed to the errors inherent in using any formula which does not involve integration. This method has added only 4.1 Gm.M. to the standard deviation which is the best we could hope to attain. The scatter is a little less than that of any method of estimating work based on the ballistocardiogram but the difference is too small to be significant. However, because the systemic arterial blood pressure is independent of events concerned with the right heart, one has the right to expect that methods of estimating left ventricular work from blood pressure alone would have an applicability extending over the whole clinical field.

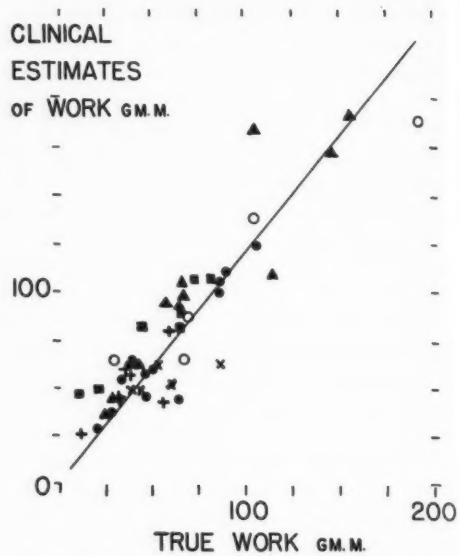


FIG. 4. Tests of clinical work estimates from peripheral blood pressure alone. The estimates were made from femoral blood pressure measurements recorded by puncture of the artery, using stroke volume formula no. 59. The data were obtained from subjects perfused with *blood*. Symbols as in figure 2. The best line shown corresponds with regression equation no. 85 of table 4. The correlation coefficient of the estimates with true work is 0.91.

This method of estimating left ventricular work from peripheral blood pressure alone could be further tested by making use of the results secured in the cadaver experiments in which water was employed as injection fluid, although the marked difference in viscosity of water and blood made it unlikely that the quantitative aspects of the two sets of results would be altogether similar. Therefore, we analysed the results secured in our sample of 63 consecutive systoles performed on the six cadavers perfused with water. Since true work, obtained by integration of the curves, had not

TABLE 4.—*Regression Equations Relating "True" Left Ventricular Work to Clinical Estimates of Work made from Peripheral Blood Pressure Measured by Arterial Puncture in the Cadavers Perfused with Blood*

Equation No.	Equations	σ Gm.M.
	When X_4 = stroke volume formula no. 59 −	
	= 91 + 0.54 pulse pressure − 0.57 diastolic pressure − 0.61 age	
85	True work $Gm.M. = -1.67 + 0.83$ [(X_4 *cc.*) (mean femoral B. P. $mm.Hg$)(13.6)(10^{-3})]	14.9
	When X_5 = stroke volume formula no. 88 of Table V	
86	True work $Gm.M. = -7.96 + 1.22$ [(X_5 *cc.*) (mean femoral B. P. $mm.Hg$)(13.6)(10^{-3})]	16.5

been determined in these "water" experiments, we estimated approximate work by multiplying the stroke volume measured in the syringe by mean central blood pressure, and compared it with clinical estimates of work made from the product of estimates of stroke volume from formula No. 59 and mean peripheral blood pressure. The dot diagram showing these results is given in figure 5 and the regression equation is given as No. 91 in table 6.

Our expectation of quantitative differences between results secured in cadavers perfused with blood and in those perfused with water is borne out by these results, for the slope of the regression is somewhat different from that found in the subjects perfused with blood, and the scatter is considerably greater. However, the increase of scatter may be due in large part to the necessity of using approximate work rather than true work as the target value. Despite this, the correlation is still highly significant and the general nature of the relationship developed in the subjects perfused with blood is clearly confirmed by the results secured on those perfused with water.

However, a limitation was encountered. In three systoles conducted in subject E. B., characterized by very high diastolic pressures, over 150 mm. Hg in two instances, and small pulse pressures, our stroke volume formula No. 59 estimated that the stroke volume was zero or less, although the actual stroke volumes were 13, 20 and 36 cc., differences which we hesitated to attribute to experimental error. Since it appeared that when diastolic pressure approached 150 mm. Hg, our method became less accurate, it was decided to look for other types of stroke volume formulas which might avoid the difficulty, a search in which we were encouraged by a friendly suggestion from Professor H. C. Burger of Utrecht.

Accordingly, results secured by a formula of the type originally proposed by Liljestrand

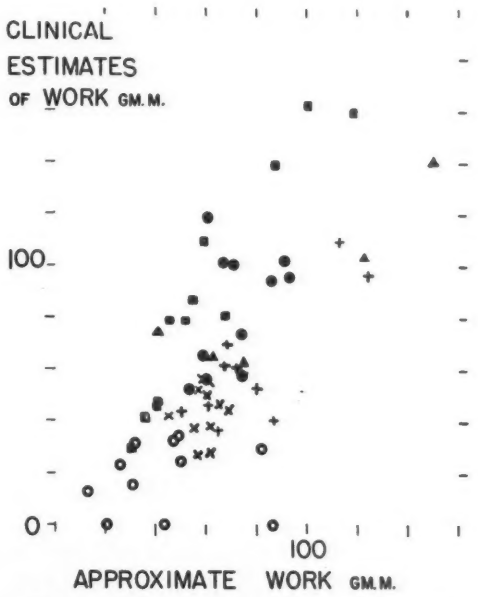


FIG. 5. Tests of clinical work estimates from peripheral blood pressure. The estimates were made from femoral arterial pressure and the subjects' age, using stroke volume formula no. 59, and mean femoral blood pressure, as in the estimates in figure 4; but the data comes from six subjects perfused with *water*. Note that the horizontal coordinate is not true work, but approximate work, estimated as the product of stroke volume and mean aortic pressure without regard to time. Data secured from the various subjects is represented as follows: dots, A. McG.; crosses, J. I.; squares, E. S.; triangles, P. L.; circles, E. B.; and X's, E. S.; The corresponding regression equation is no. 91 of table 6. The correlation coefficient between the estimate and approximate work is 0.68.

TABLE 5.—*New Regression Equations for Estimating Cardiac Stroke Volume from Peripheral Blood Pressure*

Equation No.	Equations	σ cc.
	When Z_1 = mean pressure = $\left(\frac{\text{systolic + diastolic pressure } mm.Hg}{2}\right)$	
87	Stroke volume $cc.$ = 20 + 45 $\left(\frac{\text{femoral pulse pressure } mm.Hg}{Z_1}\right)$	11.5
88	Stroke volume $cc.$ = 47 + 59 $\left(\frac{\text{femoral pulse pressure } mm.Hg}{Z_1}\right)$ − 0.58 Age *years*	9.3
	When $Z_2 = \frac{\text{2 systolic pressure + diastolic pressure } mm.Hg}{3}$	
89	Stroke volume $cc.$ = 18 + 53 $\left(\frac{\text{femoral pulse pressure } mm.Hg}{Z_2}\right)$	11.6
90	Stroke volume $cc.$ = 45 + 71 $\left(\frac{\text{femoral pulse pressure } mm.Hg}{Z_2}\right)$ − 0.59 Age *years*	9.4

TABLE 6.—*Regression Equations Relating Approximate Left Ventricular Work to Clinical Estimates of Work Made from Peripheral Blood Pressure Measured by Arterial Puncture in 63 Systoles in 6 Cadavers Perfused with Water*

Equation No.	Equations	σ Gm.M.
	When X_4 = stroke volume as estimated by formula no. 59 in cc.	
91	Approx. work $Gm.M.$ = 35.25 + 0.48 [(X_4)(mean femoral B. P. $mm.Hg$)(13.6)(10^{-3})]	18.6
	If three points giving impossible results are omitted (see text)	
92	Approx. work $Gm.M.$ = 31.70 + 0.52 [(X_4) (mean femoral B. P. $mm.Hg$)(13.6)(10^{-3})]	17.7
	When X_5 = stroke volume as estimated by formula no. 88 in table 5, as cc.	
93	Approx. work $Gm.M.$ = 23.82 + 0.56 [(X_5)(mean femoral B. P. $mm.Hg$)(13.6)(10^{-3})]	18.8

and Zander,[14] in which pulse pressure is divided by mean pressure, were compared with the measured stroke volumes in the experiments conducted on the five cadavers perfused with blood. The simple and multiple regression equations calculated by Dr. Schild are given in table 5.

Inspection of these results shows that the resulting stroke volume methods, though truly excellent when age is also considered, are not quite as good as the best of those published previously.[7] That this should be true is a mathematical necessity, for regression equations in which items such as pulse pressure and diastolic pressure (or mean pressure) are treated as independent variables must have an advantage over a formulation in which the relation of pulse pressure to mean pressure is fixed. But one notes that the loss of accuracy is very small and the newer formula might have advantages when applied to other bodies of data.

Accordingly, one of the newer stroke volume formulas, No. 88 of table 5 has been used with mean peripheral blood pressure, to provide a clinical estimate of work which could be compared with the true work. Figure 6 shows the relationship in the systoles simulated by injections of blood, the regression equation is No. 86 in table 4. Obviously the correlation is very strong, $r = 0.89$, while 0.27 is significant for $p = 0.05$. The agreement between true and estimated values is excellent, but it is not quite as good as when formula 59 was employed. A similar clinical estimate of work, made by using the newer formula no. 86 to compute stroke volume, was also compared with approximate work in the 63 systoles in six cadavers in which water was used as perfusing fluid. A dot diagram of these results is given as figure 7 and the regression equation is No. 93 in table 6. The three systoles of subject E. B. in which the stroke volume was estimated to be zero by the older formula 59, are much better handled by the newer formula; but the correlation of the data as a whole is not im-

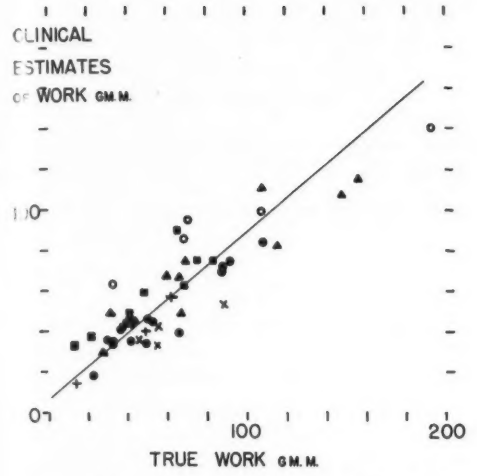


FIG. 6. Tests of clinical work estimates from peripheral blood pressure alone. These estimates were made from femoral arterial pressure and the subjects' age, using the ratio formula no. 88 to estimate stroke volume. Data from six subjects perfused with *blood*. Symbols as in figure 2. The best line corresponds with regression equation no. 86 of table 4. The correlation coefficient with true work is 0.89.

proved. By inspection of the dot diagram shown as figure 7 one sees that it is the results secured on E. S., the oldest subject studied, which disturb the correlation of the group. The values secured on E. S., although they form a beautiful regression among themselves, outlie upward and to the left of all the other data. We have no explanation for the divergence. If this subject's data are disregarded, the correlation of the rest is tremendously improved. In the data set forth in figure 5 when formula no. 59 was employed to estimate stroke volume, the results secured in E. S. do not stand as far apart from the rest, a point in favor of the formula first employed.

When inspecting figure 7, one must remember, as is the case in figure 5, that the use of approximate rather than true work as the target is certainly a considerable factor in the increase in scatter.

In short, our data do not permit us to say which of the two methods of estimating left ventricular work from peripheral blood pressure will be found superior in the clinic. Tested against data secured in cadavers perfused with blood, and in those perfused with water, in neither group are their correlation coefficients or their standard deviations about the regression significantly different. However, there is reason to suspect that the newer method may give superior results in some cases having high hypertension, and this should be kept in mind by those using these methods in the clinic.

Either of these formulas gives a test for cardiac work which, while it is a rough one, has certainly sufficient accuracy to divide human beings into three groups: those whose hearts are working normally, and those whose hearts are abnormally weak or strong. However, inspection of all the figures shows that most of the scatter is caused by differences between one subject and another, for the correlations between true work and clinical work

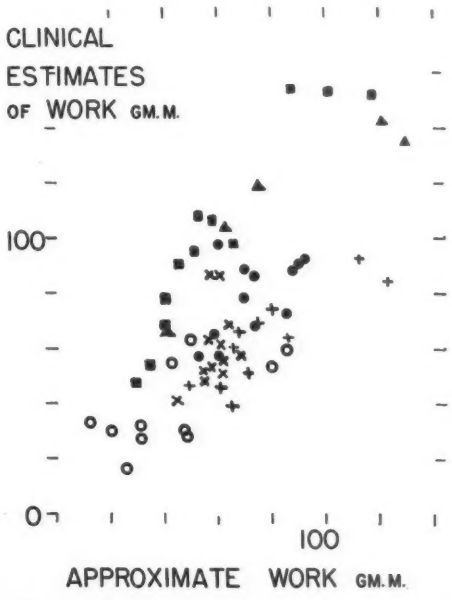


FIG. 7. Tests of clinical work estimates from peripheral blood pressure alone. The estimate is from femoral intra-arterial pressure and the subjects' age, using the ratio formula no. 88 to estimate stroke volume, a method similar to that used for the estimates of figure 6, but the data is from six subjects perfused with *water*. Note that the horizontal coordinate is approximate work. Symbols as in figure 5. The regression formula is no. 93 of table 6. The correlation coefficient between the estimates and approximate work is 0.66.

estimates in individual subjects are much stronger than those of the groups as a whole. So our ability to detect changes in the left ventricular work of any patient, due to the changing severity of disease, or to therapy, is obviously of a much higher order than is suggested by the standard deviations of the groups as a whole.

Estimations of Left Ventricular Work from Auscultatory Estimates of Blood Pressure.

The formulas discussed hitherto would serve to estimate left ventricular work from blood pressures secured from puncture of the femoral artery in any subject. Obviously, a much wider range of usefulness would be secured if these equations were adapted for use with pressures obtained by the auscultatory method as it is commonly employed. In a previous publication, regression equations relating blood pressures secured by arterial puncture with simultaneous auscultatory findings, derived from the data of Ragan and Bordley,[15] and from those of Steele,[16] were employed to permit estimations of stroke volume from auscultatory estimates of blood pressure. The use of these equations, No. 63 and 71 of a previous paper,[7] together with equations permitting estimates of mean intra-arterial pressure from auscultatory measurements, will permit estimates of work from values that any doctor could secure. If the point of muffling of sounds is taken as diastolic pressure, one uses a regression from Ragan and Bordley's data,[15] as follows:

Let X_6 = an estimate of stroke volume, as follows:

Stroke volume (cc) = 93 + 0.54 pulse pressure (auscultatory mm. Hg) −0.47 diastolic pressure (auscultatory mm. Hg) −0.61 Age years (63)

Let Y_6 = an estimate of intra-arterial mean pressure derived from equations 65* and 66,[7] as follows:

Mean pressure (intra-arterial) = −0.61 + 0.52 syst. pressure (auscultatory mm. Hg) +0.42 diastolic pressure (auscultatory mm. Hg) (94)

After solving these two equations one substitutes the results into equation 85 table

Work (Gm.M.) = −1.67 + 0.83 X_6Y_6(13.6) (10^{-3}) (8

$= -1.67 + 0.0113\ X_6Y_6$ (9

The solution of this equation estimates the left ventricular work.

If diastolic pressure is taken as the point of disappearance of sounds, regression equations derived from Steele's data[16] are similarly employed. That for stroke volume has already been published[7] as equation 71. To get mean pressure, we needed a regression equation for systolic pressure so the following was estimated from Steele's data,[16] it has not been published previously.

Systolic pressure (intra-arterial, mm. Hg) = 10.62 + 1.00 systolic pressure (auscultatory, mm. Hg) (96)

and for this regression σ = 12.5 mm. Hg. The corresponding equation for diastolic pressure has already been published[7] as equation 70.

Therefore, to estimate work from auscultatory measurements, using the disappearance of sounds as the indication of diastolic pressure, let X_4 indicate the estimate of stroke volume, as follows:

Stroke volume (cc.) = 101 + 0.5 pulse pressure (auscultatory mm. Hg) −0.59 diastolic (auscultatory at disappearance of sounds, mm. Hg) −0.61 Age (years) (71)

Let Y_4 indicate the estimate of mean pressure, as follows:

---

* A typographical error has been found in equation 65 as given in our previous communication,[7] the minus sign before the first term on the right side having been omitted. This equation should read:

Systolic pressure (intra-arterial) = −6.08 +1.04 systolic pressure (auscultatory) (65) Equation 65 has not been used previously, so the erroneous rendering did not effect any of our published results.

This seems a proper occasion to correct another typographical error. In table 3 of a previous publication[6] the femoral diastolic pressure of curve No. 2, given as 85 mm. Hg, was actually 58 mm. Hg. In calculating the regression equations of that paper we used the correct value.

Mean pressure (intra-arterial mm. Hg) = 3.21 + 0.5 systolic pressure (auscultatory mm. Hg) +0.52 diastolic pressure (auscultatory at disappearance of sounds, mm. Hg) (97)

After solving these equations, one substitutes the solutions X_4 and Y_4, for X_6 and Y_6 in equation 95 given above, and solves to obtain work. Jackson's nomogram[17] may be used to solve equation 71.

Those choosing to use the *pulse pressure* to *mean pressure* ratio, equation 86 of table 4, as the basis for an estimate of work, could readily convert it for use with auscultatory pressures by making use of the appropriate equations given above.

Anyone accustomed to the use of a slide rule will have no difficulty with the computations needed to estimate heart work from blood pressure, although they may look complex at first glance. Our attempts to simplify the formulas have led to an interesting line of inquiry too long to be presented in this paper.

Before leaving the subject, gaps in our knowledge must be once more pointed out. In converting to permit the use of blood pressure measurements by the auscultatory method, we are assuming that intra-arterial pressures in the brachial and femoral arteries are similar. We have discussed the size of the error;[7] if it exists at all it is small. But, while we do not know of data proving that these two pressures are significantly different, there is a trend in the results[18] that suggests that estimates of cardiac work or stroke volume, made from our formulas, adapted for measurements of blood pressure by the auscultatory method, may eventually be found a little low.

Also, we lack data on subjects in the younger age groups. The reason for our difficulty is plain enough; young people seldom come to necropsy and when they do, because of the tragedy connected with untimely death, the case is of great interest and concern to clinician and pathologist, and is not likely to be turned over for our unorthodox investigations. Nevertheless, it is of great interest to accept the extrapolation involved and employ our formulas in the clinic on all adults until better data can be secured. The majority of people with cardiovascular disease fall into the age range covered by our data.

It also seems obvious that our formulas designed to estimate cardiac work, although successful in adults without making allowance of differences in size of the subjects, should not be used in children without further study.

Applications of the Method.

It seems evident that clinicians, employing the apparatus and technic they already possess, can make quantitative deductions about the work of the hearts of their patients with an accuracy far greater than we had thought likely, and certainly as good as that of many methods on which practitioners of medicine are accustomed to rely. Therefore, it seems proper to close this communication by giving an example of one way the new knowledge may be used to illuminate familiar observations. Taking the average blood pressures at each decade of life from Hunter's compilation of observations made in a quarter million healthy Americans,[2] we have computed the average left ventricular work by means of formula 95 for each decade of adult life; the results are in table 7. Obviously the average heart's work declines steadily as age advances, even though health is maintained. Estimations of blood pressure such as these have been before the profession for many years, but the interpretation of these data in terms of the heart's work is new, and to us it seems most illuminating, as so many doctors have the impression that when blood pressure rises the heart's work must be increased. So it seems

TABLE 7.—*The Average Left Ventricular Work per Beat of Healthy Americans at Rest, as Age Advances. Estimated from Hunter's Data on the Average Blood Pressure at Different Ages*

Age Decade Years	Average Blood Pressure mm. Hg	Left Ventricular Work Per Beat Gm.M.
20	120/80	68
30	123/82	62
40	126/84	57
50	130/86	50
60	135/89	45

most likely that the methods described in this communication will also shed new light on the strength or weakness of the hearts of many patients coming to the clinic.

Summary

(1) Curves of cardiac ejection at each instant of systole, and curves of blood pressure at the root of the aorta, secured in experiments in which systole was simulated in cadavers, have been used as the basis of a precise estimate of "left ventricular" work by integration. The results of these precise estimates have been called true work, and it seems obvious that they far exceed in accuracy any estimates of left ventricular work that have been made in living men or mammals.

(2) Results secured by the method of estimating work commonly employed by physiologists, based on the product of stroke volume and mean pressure, have been compared with true work. This method gives a good approximation of the true work. Regression equations which would improve such estimates have been derived.

(3) By computing simple and multiple regression equations, we have sought means of estimating true work from measurements which could readily be made in the clinic. Such clinical estimates of work, based on the ballistocardiogram and intra-arterial measurements of peripheral blood pressure, or on peripheral blood pressure alone, have been compared with true work. In the best of these methods, in two-thirds of the estimates, the error is less than 22 per cent of the average level of cardiac work per beat of healthy young adults at rest. This accuracy seems sufficient for many clinical purposes, such as dividing the population into groups which are normal, above normal or below normal as regards left ventricular work.

(4) The data clearly show that the chief cause of the scatter in such clinical methods is due to differences between individuals. The ability to detect changes in the cardiac work of most individuals greatly exceeds that indicated by the figures given above.

(5) Formulas have been derived which permit estimates of left ventricular work from auscultatory measurements of blood pressure, so that rough estimates could be made by anyone practicing medicine.

(6) By means of the average values for blood pressure of healthy Americans at rest, and the formula mentioned above, average left ventricular work has been estimated for each decade of life from 20 to 60 years. Despite the well known rise in blood pressure, the average heart work declines steadily as life advances. At 60 years of age the average work per beat is about two-thirds of the average found at 20 years of age.

Summario in Interlingua

Le labor "sinistro-ventricular" pote esser estimate con un alte grado de exactitude in experimentos con cadaveres in que curvas de pression e curvas del ejection cardiac es registrate pro omne punctos del systole. Considerante tal exacte estimationes como criterio in le evalutation del resultatos, nos ha interprendite le cerca de methodos que permitterea le estimation del labor cardiac super le base de mesurationes de un genere executabile in le clinica.

Nos ha succedite a derivar formulas que permitte le estimation del labor sinistro-ventricular super le base de mesurationes auscultatori del pression sanguinee. Assi iste methodo pote esser usate per omne practico medical.

REFERENCES

[1] Starr, I., Collins, L. H., Jr and Wood, F. C.: Studies of the basal work and output of the heart in clinical conditions. J. Clin. Invest. **12:** 13, 1933.

[2] Best, C. H. and Taylor, N. B.: The Physiological Basis of Medical Practice. Ed. 6, Baltimore, Williams & Wilkins, 1955.

[3] Frank, O.: Die Grundform des arteriellen Pulses. Zeitschr. f. Biol. **37:** 511, 1898.

[4] Katz, L. N.: Observations on the external work of the isolated turtle heart. Am. J. Physiol. **99:** 579, 1932.

[5] Starr, I., Schnabel, T. G., Jr. and Mayock, R. L.: Studies made by simulating systole at necropsy. II. Experiments on the relation of cardiac and peripheral factors to the genesis of the pulse wave and the ballistocardiogram. Circulation **8:** 44, 1953.

[6] — and —: Studies made by simulating systole at necropsy. III. On the genesis of the systolic waves of the ballistocardiogram. J. Clin. Invest. **33:** 10, 1954.

[7] —, —, ASKOVITZ, S. I. AND SCHILD, A.: Studies made by simulating systole at necropsy. IV. On the relation between pulse pressure and cardiac stroke volume, leading to a clinical method of estimating cardiac output from blood pressure and age. Circulation **9:** 648, 1954.

[8] —: Units for the expression of both static and dynamic work in similar terms and their application to weight-lifting experiments. J. Appl. Physiol. **4:** 21, 1951.

[9] ASKOVITZ, S. I.: Rapid method for determining mean values and areas graphically. Science **121:** 212, 1955.

[10] STRAUB, H.: Das Arbeitsdiagramm des Säugetierherzens. Pflüger's Arch. f. d. ges. Physiol. **169:** 564, 1917.

[11] STARR, I. AND SCHNABEL, T. G., JR.: Studies made by simulating systole at necropsy. V. Estimation of the contour of the left ventricular ejection curve by an adjusted integration of the aortic blood pressure curve. J. Appl. Physiol. **7:** 273, 1954.

[12] —: Studies made by simulating systole at necropsy. VI. On the estimation of cardiac stroke volume from the ballistocardiogram. J. Appl. Physiol. In press.

[13] TANNER, J. M.: Normal standards for cardiac output in man. J. Clin. Invest. **28:** 567, 1949.

[14] LILJESTRAND, G. AND ZANDER, E.: Vergleichende Bestimmungen des Minutenvolumens des Herzens beim Menchen mittels der Stickoxydulmethode und durch Blutdruckmessung. Ztschr. ges. exper. Med. **59:** 105, 1928.

[15] RAGAN, C. AND BORDLEY, J., III: Measurements of blood pressure. Bull. Johns Hopkins Hosp. **69:** 526, 1941.

[16] STEELE, J. M.: Measurements of arterial pressure in man. J. Mt. Sinai Hosp. **8:** 1049, 1941–2.

[17] JACKSON, C. E.: Nomogram for simple calculations of cardiac output. Circulation **11:** 635, 1955.

[18] KOTTE, J. H., IGLAUER, A. AND MCGUIRE, J.: Measurements of arterial blood pressure in arm and leg. Am. Heart J. **28:** 476, 1944.

Dynamic Comparison of Current Ballistocardiographic Methods

Part III. Derivation of Cardiovascular Force from Body Motions

By S. A. Talbot, Ph.D., and W. K. Harrison, Jr., M.E.

In part I was discussed the nature and magnitude of force artefacts in the ballistocardiogram (BCG) arising from coupling the body to ground. The effect of this grounding on the reading of cardiovascular motion, momentum and force was explained, using the simple one-mass dynamics. Part II dealt with the effects on the ballistocardiogram of a second mass, a platform supporting the body. The body itself is a cutoff filter (of the resonant type) by its springy supporting tissues which couple the body and platform masses. In the displacement ballistocardiogram this attenuates the upper frequencies recorded from stiffly sprung platforms, or from the direct-body whatever its coupling to earth. In the acceleration record, the body mass and spring cut off the lower ballistocardiographic frequencies, while platform mass and body-spring cut off the higher frequencies. The size of these errors and their bearing on multilateral recording were discussed.)

In part III we examine the proposition that from a ballistocardiograph record, we can derive a picture of the cardiovascular forces. If a simple resonating filter is interposed by the body and/or the platform, does present knowledge let us take this into account, and still derive the cardiovascular force pattern from the ballistic motions?

In parts I and II we assumed the body to be a single unitary mass, responding at all frequencies to a fixed pattern of cardiovascular force applied directly to it. If so, this *force* pattern should be recorded fairly uniformly from 1 to over 30 cycles per second by the acceleration ballistocardiogram taken from light, weakly sprung platforms like those of Burger and v. Wittern; for frequencies below about 4 cycles per second by the displacement ballistocardiograph of Dock and Starr; and for higher frequencies only, by the acceleration ballistocardiograph of Smith. Below about 15 cycles per second, this basic assumption appears approximately valid when tested by a *shaker* applied externally to the *whole* body. However, if a shaker is applied to the head, chest[2] or feet[34] the body does not move as a whole, so that the resonance and damping factors change. Even more, when considering the actual cardiovascular drive from within, we may legitimately doubt the adequacy of the two-mass analysis used by Nickerson, Burger, v. Wittern and ourselves, to get at the actual ballistic forces.

A quite direct test of these assumptions when applied to the actual internal drive, would be simply to *remove* from the ballistocardiogram the predicted distortions arising from the interaction of the body mass and its support. In this way, the displacement record, $\frac{y_b}{F_b}$ should become that of mass m_b alone unimpeded by k_b, r_b, or m_p, k_p, r_p. In technical parlance[25, 33] the body-platform system "operates" on the driving force F_b with a complex "transfer function" $y_b(f)$; we can simply invert this "operator" to discover the original force pattern: $F_b y_b \times 1/y_b = F_b$. If the assumptions of a two-mass model and directly applied force* are valid, one can readily set up the inverse of the very specific mechanical distorting mechanisms described in part II for each kind of support, eliminate the distortions, and find an "internal ballistocardiogram" or force-on-body (F_b). For a given subject, this force pattern should be the same whatever the support, and agree with the ballistocardiogram taken on a support which is free of the distorting constraints: e.g., the mercury bed

* Part I of this article, Circulation **12:** 577 (Oct.) 1955.

v. Wittern[33] first used this approach quantitatively for the direct-body method (single mass system). He passed the velocity ballistocardiograph signal through an electric network whose dynamic parameters were inverse to those of his subject referred to the support, and derived the subject's intrinsic "force ballistocardiogram" pattern. This force (F_b) he sought to explain in terms of simpler force patterns from the heart as the generator, via internal mechanical networks which might account for the details observed.

This method of inverse correction was also applied by Tobin and colleagues,[53] to both the displacement (D) and velocity (V) direct-body ballistocardiograms. The similarity of the two ballistocardiograms, after correction for body resonance, was interpreted as proving the adequacy of this correction. Actually, this similarity results from D being the integral of V. In a later paragraph we will discuss the adequacy of this method.

The inverse network has not been applied to the platform methods in current use clinically. To do this, the signal from the patient need only be passed through a network like that of figure 2*C*. The network becomes *inverse* by connecting it as the feedback in a gain-of-one amplifier. Insertion of the m_b r_b and k_b for each patient and m_p r_p and k_p for the platform (if any) would give a final record purporting to be his unique *force ballistocardiogram.*

Nickerson[25] has published an approximate method of inverse correction[A9] for several current ballistocardiograph systems, using graphically the "transfer operator" method described above. For each of seven subjects he worked out the frequency spectrum of the displacement ballistocardiogram from four different supports, and corrected these by applying inversely the respective transfer curves; similar to those in figures 3 and 4. For each subject, the corrected ballistocardiograph force spectra did show considerably less deviation from the mean than before correction; the mean was best approximated by the force spectrum as computed from the Nickerson bed. This convergence of the force patterns suggested a common basic "force ballistocardiogram" for each individual: i.e.,

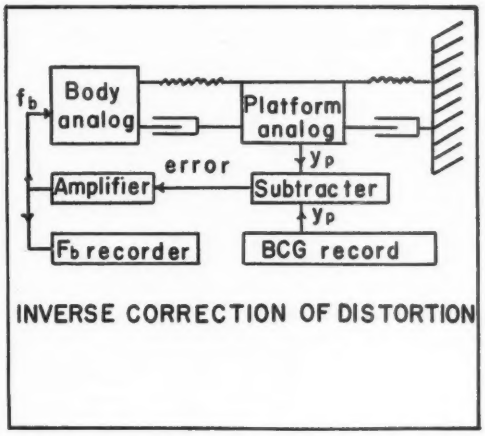


FIG. 8. Schematic drawing, showing principle of inversely computing and recording the force pattern which will so drive equivalent body-bed system as to produce observed ballistocardiogram.

that one can indeed remove the distortion in part by using the simple two-mass analog in reverse. The results were presented in the form of spectra. The task of recovering the "force ballistocardiogram" (vs. time) from these spectra by summating sine curves (corrected for phase) is formidable and was not carried out. Hence our results do not compare directly with the "force ballistocardiogram" derived in this way: by passing through the frequency realm.

In general, our method of deriving the "force ballistocardiogram" from the distorted record involves feedback and an electrical analog whose parameters are those measured for the body and bed. The inverse network (v. Wittern's method) is not used, but instead the direct analog (fig. 2*C*) is so *driven* (fig. 8) that its output exactly equals the subject's ballistocardiogram (fig. 8). It results in general that the "force ballistocardiogram", derived by deleting in this way the distortions from forces between body and support, does not really emerge as a single pattern characteristic of our subject, but differs significantly as between methods. That is, *correcting* a ballistocardiogram for the distortions shown by one or two-mass dynamical theory does *not* yield a record which one is

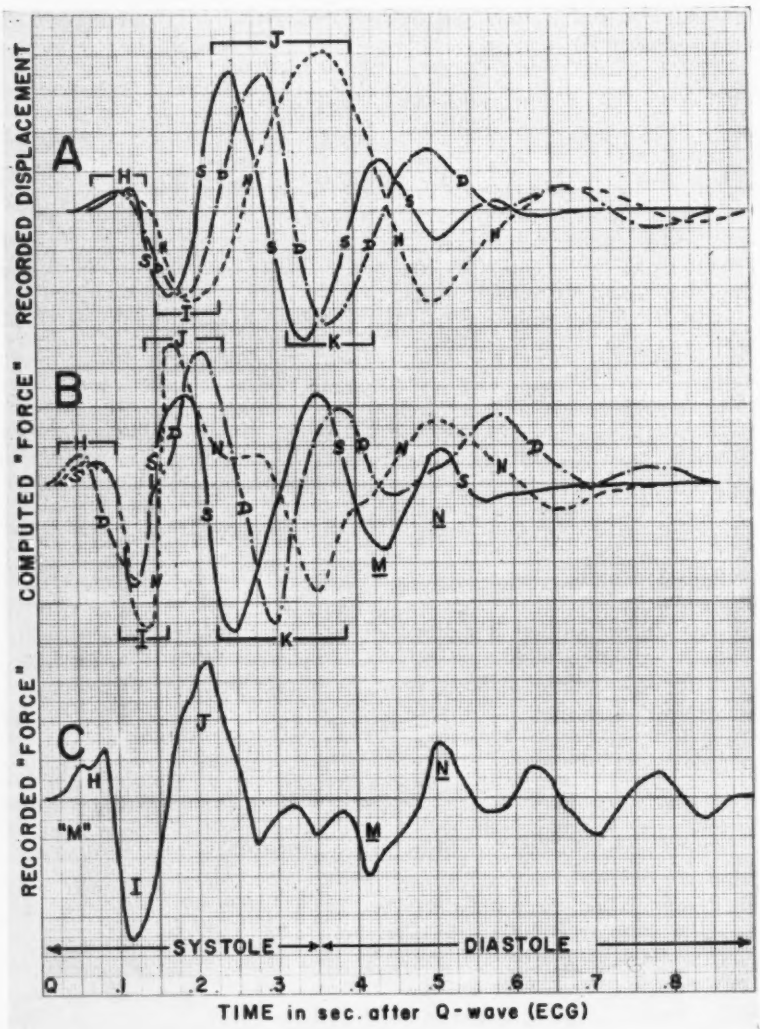


FIG. 9. *Correction of Ballistocardiogram for Mechanics of Body and Support. A.* Displacement tracings of one person using methods of Starr, Dock, Nickerson. *B.* Same, corrected for body and platform artefacts by "inverse" computation of force (method of fig. 8). Note phase-inversion of forces in B (S, D), showing ballistic force pattern to be mainly more rapid than measured body frequency. *C.* "Force ballistocardiogram" recorded from same person with the less distorting mercury bed "M". This resembles "computed force" from N method, of next least constraint. Note sharp tips and jogs, showing higher frequencies, difference of systolic complex from tracing A (S, D), and nonuniform phase shift of peaks.

really justified in calling a "force ballistocardiogram". The reason for this will be discussed, and where it leads.

METHOD

This part of the study was completed[28] before we found electric analog components of a quality which could be operated in the simple method shown in figure 8. We employed instead a (Reeves) differential analog computer. This sets up the mathematical equations (part II, Equation 2) term by term for the voltage y_p (F_c),* eliminating y_b alge-

* Notation as introduced in Part I.

b:aically and using the stated body and bed parame-t:rs. A cathode-ray function-former converted the s:bject's displacement ballistocardiogram taken f:om the bed or body into an electrical signal; t is was then equated to the voltage $y_p(f)$ by the f:edback method (fig. 8). The curves of F_b so :itten were then changed to the time scale of f:gure 9, the amplitudes (before computation) :qualized, and the same subject's (mercury-bed) :celeration ballistocardiogram* added.

In this way, we have "corrected" the ballisto-:rdiograms of the same subject from each of three l:dy supports: the (original) Nickerson bed, the (Johns Hopkins) Starr bed, and directly from the s:ins (Dock method). The body parameters were measured each time since the stiffness and damping differ with pressure on the footboard.

Results

Figure 9*A* shows the subject's ballisto-cardiograph records, figure 9*B* the body force pattern F_b, computed as prior to distortion by the various supporting systems and figure 9*C* the ballistocardiogram force pattern from a system whose distorting constraints are minimal i.e., the acceleration of a very light ballistocardiograph platform floating on mercury.[12] (1) The derived "force" pattern for all three methods turns out to be considerably earlier than that of the original displacement ballistocardiogram, even when these ballisto-cardiograms purport to measure "force".[2, 3, 6] (2) The stiff-bed ballistocardiograph response, "S", is earlier than the direct-body "D", but the computed "force" pattern is not dissimilar. (3) The soft-bed ballistocardiogram, "N", whose displacement record is much retarded, gives a computed "force" record as early as the two stiffer mounts. (4) The "force" producing the "S" and "D" records shows strong systolic events at K (0.25 second) and L (0.35 second), which do not occur in the lowest force record, "M", (fig. 9*C*). However, the force pattern, "N", more closely resembles the force "M" and includes the headward early diastolic wave 0.5 second after Q. (5) The mercury bed ballistocardiogram "M" like the light pendular beds[16, 23] contains characteristic high frequency details (sharpness, jogs and riding waves) which were not recorded in any of the original displacement records of this subject.

Discussion

Several aspects of the results observed (fig. 9) are quite to be expected, and show the general improvement[25, 33] of the force ballisto-cardiogram obtained by grossly correcting the main distortions from the support. For example, (1) removing the predicted phase shift at resonance (fig. 3*A*) from all three records results in a "force ballistocardiogram" which (for the I and J peaks) is earlier for all three methods. This shift is not small (60 milliseconds), in fact almost suffices to invert the pattern (fig. 9*A* to 9*B*). It is as if the frequency of the cardiovascular impacts lay enough *above* body resonance to make the displacement *opposite* to the force (180 degree phase shift). (2) Since the main dynamical difference of the S method vs. the D method is the increased body-frequency due to the footboard, the "force ballistocardiogram" derived for both is much alike. The differences between them may tentatively be assigned to the difference in the "look" at the ballisto-cardiogram: the S method "looks" through joints under compression, and through a direct dorsal coupling as well; the D method "looks" through a loose distal coupling only. The prevalence of late irregular diastolic vibrations in the D record is another sign of this looseness. (3) Nevertheless, the S and D *force* patterns still contain "ringing" or spurious after-waves at 0.27 and 0.37 second. The correcting system, using the measured body parameters, could not remove these. v. Wittern[33] also observed this for the D pattern.

* Since the feedback amplifier shown had a gain of 50, the output of the network driven by F_c matched the potential derived from the recorded ballistocardiogram within 2 per cent. The Reeves computer operates 20 times slower than the true ballistocardiogram but is rather complex to adjust. The method of figure 8 adjusts easily but operates 10 times faster and requires a speeded-up transcription of the ballistocardiogram. It should not be attempted without inductors whose Q exceeds 10 at 5 cycles per second (Hycor Company, Pasadena, Cal.)

The large number of RC elements used in a differential computer introduces a strong phase shift of frequency components above 50 cycles per second which would cause instability (oscillation) if not attenuated down to the noise level by a high-cut filter. The filter used introduced an overall phase lag of 20 milliseconds, which was corrected.

The corrected "force" record of Tobin and colleagues,[53] while more successful than our corrected curve D (fig. 9*B*), still retains an excessive K dip as well as the characteristic periodicity caused by supports of the Dock and Starr types. This suggests that the dynamic parameters measured by the external tap method, do not adequately measure the inertial, spring and viscous coefficients of the body *as driven from within*.

(4) The displacement record of Nickerson does not really measure *force* on body, as has been explained (part II). However, confirming Nickerson,[25] the force *computed* from it most closely resembles the force recorded from the unresisting bed M. We may conclude that a platform whose soft springs permit it to follow the body well, i.e., minimally excites the dorsal springs and dampers, *conserves* the best force information for a subsequent correcting device. Conversely, the stiffer D and S supports seem to *complicate* the body motion, away from a simple oscillator's behavior, so that their ballistocardiograms are *less correctable* on this dynamical assumption. (5) The mercury-bed acceleration ballistocardiogram (M, fig. 9) we consider as good an approach to a "force ballistocardiogram" as can be obtained at present from sensing the motion of the body as a whole. The body springs and dampers are activated[12] minimally, and the inertial reaction of the platform (11 pounds) is relatively small (fig. 7). Although, as with all body mounts, the *mass* of the body which moves with the recorded acceleration, $\ddot{y}_p$, *varies* with frequency, a "force" derivable from the simplified relation $F_c = m_b\ddot{y}_p$, with m_b taken constant and no other terms, is still the least distorted picture of cardiovascular force pattern to be had by whole-body ballistocardiography. A well designed pendular mount[23] gives almost exactly the same detail. This is our justification for using the lowest record as a basis for judging[29] the directly recorded ballistocardiograms as well as the corrected "force" patterns D, S and N computed from them.

The *phase* relation of the M record (fig. 9*C*) to the displacement ballistocardiogram above (9*A*) gives further evidence that the vibration properties of the body cannot be corrected by assuming that it acts as a simple oscillator, with any exactness. The J peak of the directly recorded force ballistocardiogram "M" stands intermediate between the displacement (fig. 9*A*) and computed force (fig. 9*B*). Evidently the inverse network of a "simple" body oscillator overcompensates for phase.

Errors in the Assumptions of Whole-Body Ballistocardiography

Three explanations can be offered for the difference of "force" patterns (fig. 9*B*) calculated as driving the same body on the different supports. These are: I the complex-mass effect, II the loading effect and III the summation effect.

I. The body mass is complex in two ways: (1) as regards coupling to the platform and (2) as regards internal coupling. Referred to a plane supporting the whole body, the legs and thorax have separate resonant modes of vibration, due to separate masses and different stiffness of contact at shoulders, hips, thigh and feet. A shoulder clamp[5] may further complicate the system, by cancelling high frequency components working in opposite phase at feet and shoulders. Similarly, several other discrete masses (e.g., liver, intestines, thighs, whole limbs) are variously coupled to the skeleton which drives them, and move out of phase at higher frequencies, though damping may prevent any local resonance effect. These parallel coupled loads[33] were used to account for the excessively broad peak of body resonance recorded on our shaker table with footboard (fig. 2).

This factor would operate as follows, with change of ballistocardiograph support (D, S, N, fig. 9). A light platform, with negligible springs, excites but little elastic reaction at the places of body contact; but heavier platforms or increased rigidity of support bring into the record these vibratory complexities, and vitiate the simple two-mass analog. Similarly, as the parts coupled to ground become more fixed by increasing constraint, (i.e., with coupling as stiff as that used in the direct-body and sand-bed methods), the looser internal masses mentioned will begin to oscillate separately, further breaking up the body

unity and further altering the analog. The ballistocardiograms of these various systems, therefore, do not refer to the same vibratory configurations, and should not be expected to agree in detail. The most "standard" mechanical state, then, would be that in which forces on the body from the support (in the direction of recording) are *minimized*.

II. The *loading* effect is distinct from the complexity of the body masses, and the various ways in which differing supports will actuate this complexity. This factor, well known in system design,[14] depends on energy absorbed by the part driven. Thus the heavy Nickerson platform has a velocity comparable to the body's; this takes kinetic energy, and increases the phase shift of platform and body referred to the drive (fig. 3*A*). But because of their different mass and damping, the platform and body move with velocities which differ with frequency. This *relative velocity* makes them drag or load each other. With the Starr support, the platform gets relatively little velocity (10 per cent) and draws rather less energy $\left(\frac{mv^2}{2} = 1 \text{ per cent}\right)$. In the direct body method, the table shares negligible velocity, and so does not "load" (distort) the body motion by this consideration at all. But without footboard, the legs do exhibit considerable velocity (phase lag) relative to the thorax,[33] absorb kinetic (loading) energy, and so should drag the thorax out of phase with the driving force. Other submasses of the body (e.g., liver) exhibiting appreciable out-of-phase velocity at higher frequency, will similarly load their couplings and so contribute to the differences in the ballistocardiograms recorded on different supports. Error due to loading is reduced by less velocity across couplings: which points again to a light platform, lightly hung, with footboard.

This "loading" does not affect the *original* force pattern exerted by the moving cardiovascular masses, because of the relative inertias involved. Conservation of momentum shows that the average *velocity* of motions in the body are around $\frac{1}{1000}$ that of the blood at any instant. The kinetic energy drawn by the body is correspondingly small; adding a platform would negligibly affect the source. This *loading* effect is important to the physiology of the ballistocardiograph, because the cardiovascular forces observed depend on the reaction of the surrounding tissues and body. If the body is relatively immobile, the loading (in the mechanical sense) is least, and the acceleration of blood exerts its greatest bodily force. In an open chest, the cardiovascular forces see less impedance, the vessels move more and blood less, relative to them, so that the forces on the body are reduced.

III. Related to both the change of mass configuration and the emergence of relative velocities in the body, is the change of output *summation* with frequency. Below 6 cycles per second, the shins may well represent the thoracic motion; at higher frequencies they are highly sensitive to the leg support, summating the drive (from above) and constraint (from below) in quite a variable way.

A Starr-type platform sums the forces generated at the major contacts, according to how excitation and phase of the tissue-spring force at each contact, relate to the platform-spring reaction. This applies equally to the lightest platforms, which can be shown[26] to average out the headward and footward motions of thorax and feet due to respiration.

All of these errors from whole-body recording, point toward detachment of our thinking of "the body as a whole": the concept that we can in any accurate way measure a simple force on "the body" by measuring "its" displacement or acceleration. The attempt to do so leads to records which are not comparable between methods, and between workers with the same method differently adjusted. Distortion from varying mass-complexity may possibly be reduced by recording from thorax alone, with precautions not yet known. Distortion from loading may be reduced by separate platforms for thorax and legs, servo driving to reduce the inertial reaction and other dynamic precautions. Summation error can be reduced by including less of the passive body masses in the sum.

In summary, we should reduce the number and complexity of passive elements through which the ballistocardiogram is seen. As these

irrelevancies are reduced, statistical scatter should be reduced also, and the observed motions of a given individual should correlate better with his detailed cardiovascular dynamics.

General Conclusions

(1) *Physical.* The effort to use our understanding of one- and two-mass vibratory systems inversely to *compute* an individual's "true ballistic force" pattern (F_b) is not wholly successful. Not one, but several "true" F_b curves emerge, according to the body supports in use. The differences are systematic, not merely random. This failure of the two-mass body-bed analog is attributed mainly to the breakdown of vibratory unity, especially above body resonance. In addition, the contribution of these smaller masses varies, because their *coupling* depends on the constraints and loading by the support. The simple concept of a two-mass chain omits such variable internal coupling factors.

As the constraints are reduced (e.g. Nickerson method) the force pattern, F_b, computed from the displacement ballistocardiogram approaches the acceleration pattern from the mercury bed. However, most of the ballistic information is simply omitted from the displacement record because the body mass acts as a high-cut mechanical filter in all methods in current use. The faster details, once attenuated into the "noise" level, cannot be recovered by the method of inverse correction. On the whole it seems better to use supports whose constraints do not appreciably select or distort the ballistocardiogram in the first place, e.g., light pendular or fluid supports.

Because of these factors, one should not identify with *cardiovascular* force either this computed driving force (F_b) or any of the force ballistocardiograms interpreted from present whole-body methods. Until the transmission system of the body components is studied, as well as the actual forces being generated at their several origins in the living system, this identification seems unwarranted.

The emphasis in this paper on the contribution of somatic transmitting elements to the head-foot ballistocardiogram, does not imply disregard of other major problems. Hardly mentioned here is the importance of analysing the *components* of the ballisto-cardiographic pattern. Each event, even when properly recorded, arises from a composite of discrete but overlapping physiological forces whose relative magnitude can change in pathologic states. Furthermore, their intrinsic directions are variable and only partly in the head-foot direction. The cardiovascular forces should no more be judged from a unidirectional ballistocardiographic record than an electrocardiogram from a single lead. The application of proper mechanical principles to lateral and anterior-posterior recording, as well as studies of blood-forces at their origin, are therefore problems as important as further removal of irrelevancies from the head-foot record.

(2) *Clinical Application.* If the mechanical unity of the body usually assumed were a good approximation, one could use it practically to find the cardiovascular force pattern. Failing this unity, one may ask why a body-platform analog should be used at all. The two-mass model does seem justified as a practical way to compare the properties of various ballisto-cardiographic supporting systems used clinically. Some system must eventually be selected as the method of choice. Our analysis shows that all the methods hitherto used clinically cause irreversible distortions not only of body motion, but of the cardiovascular force pattern as well, and pass but a small fraction of the information available. The analysis also points to the design of simple supports which minimize the coupling to ground, however complex may be the force generator and the somatic transmitting system which it drives. These simplifications become more essential, as we move to include the other vector components both of the cardiovascular force and of the dynamics in bodily transmission.

In a clinical framework larger than ballisto-cardiographic methodology, the major need is to reduce the scatter in normal ballistic wave form, and the high incidence of false abnormals which reduce the diagnostic value of individual records. Insofar as this scatter and abnormality can be attributed to irrelevancies in the bodily transmission and support, such

matters deserve intensive study. So far, this study has shown (1) how and why errors from ground forces can be reduced, and (2) that with this, a much wider force spectrum can be recorded: i.e., that the characteristic ballistocardiographic record has much more usable detail.

Such additional information can lead to confusion, if handled simply by correlation with disease. Further study is needed to see what aspects are cardiovascular, and what is still body artefact. Clinical studies can then lead to new definitions of the normal, in the displacement, velocity and acceleration ballistocardiograms. The task then remains of explaining the normal and abnormal details in terms of the composite cardiovascular functions which evoke them.

We should be warned by progress so far, against trying to stabilize methodology for clinical purposes at the present level of understanding. With the electrocardiogram, the transmission of electric forces is relatively free enough of bodily complexity, to attribute the records mainly to the heart. With the ballistocardiogram, the generator itself is not unitary, the transmission is complex, problems of the support unavoidable, and more diverse among different subjects. To "clean up" this situation for clinical purposes, we may still expect a protracted period of improving methods and interpretations. The end justifies the effort, from the statistical evidence that the ballistocardiogram contains in potentially distinguishable form, unique information on the functional state of heart and vessels.

Summary, *Part III*

(1) The cardiovascular "force pattern" of a single individual may be derived from his records taken by direct-body, Starr bed, Nickerson bed and mercury or pendulum bed. These patterns are not the same, but the soft Nickerson bed alters the forces less than the stiffer supports.

(2) The differences are attributed (a) to the inapplicability of the two-mass analysis, as used (inversely) to calculate the force pattern, and (b) to actual differences in the cardiovascular forces exerted on the body parts when different supports (couplings to ground) change the excitation of the different internal couplings from cardiovascular system to body parts.

(3) The simple one- and two-mass theories fail to eliminate the effects of supports, and arrive at a consistent "force ballistocardiogram," because (a) at relatively low frequencies, the body begins to oscillate *in parts*, (b) the platform (shin or bed) sees these motions in different *summation*, depending on relative activation of dorsal or other coupling springs, (c) each type of support *loads* the body couplings in a particular pattern, depending on the relative velocity of the support or platform.

(4) Because of these complexities, it is concluded that the amount of irrelevant information and scatter in the ballistocardiogram would be minimized by reducing the forces from the support. The softest supports (mercury, pendulum) introduce the least complications; but may themselves be improved by departing from whole-body recording and the whole-body interpretation of the ballistic forces.

Acknowledgments

We take pleasure in acknowledging our indebtedness to Dr. Wm. F. Follin, Director, and Dr. Bruce Lamb and Dr. Angela Kukustis of the Computing Laboratory, Johns Hopkins Laboratory of Applied Physics, in the design and operation of the inverse computation experiment; to Commander D. E. Goldman of the Naval Medical Research Institute for advice on electric analog computers; to Dr. W. W. von Wittern for much criticism and discussion; to Dr. John Nickerson for cooperation in the use of the Columbia University ballistocardiograph bed; to Dr. H. C. Burger in regard to high frequency errors; and to Dr. J. E. Smith and Dr. R. Rosenbaum of the Civil Aeronautics Authority for illuminating conversations about tuning the shin couplings. Dr. W. R. Scarborough has helpfully criticized the relation of this analysis to clinical ballistocardiography, and furnished many essential corrections. Mr. Lester W. Reynolds constructed the Starr-type bed and the shakers used.

Summario in Interlingua

Le validitate del assumption fundamental que le corpore representa un sol massa es examinate experimentalmente per un methodo que deberea cancellar le errores resultante del

varie typos de supporto. Le "ballistocardiogramma a fortia" que es assi derivate se monstra differente pro le differente supportos. Isto demonstra que le assumption fundamental non es valide. Il appare que un augmento del constringimento exercite per le supporto resulta in un augmentate complexitate del oscillation del corpore. Isto adde irrelevante detalios al desirate information cardiovascular. Il seque que le supportos que causa resonantias in le banda ab 4 a 10 cyclos per secunda (methodos a tibia e a arena) introduce le plus importante errores; le supporto de Nickerson, que es plus molle, resulta in errores minus seriose; e le errores del methodos a pendulo es le plus negligibile. Es discutite le rolo de fractionation corporee, de summation del platteforma, e del energia de accopulamento.

References, *Part III*

[30] Scarborough, W. R., Davis, F. W., Jr., Baker, B. M., Jr., Mason, R. E. and Singewald, M. L.: A review of ballistocardiography. Am. Heart J. **44:** 910, 1952.

[31] Starr, I. and Maycock, R. L.: On the significance of abnormal forms of the ballistocardiogram. Am. J. M. Sc. **215:** 631, 1948.

[32] Brown, H. R., deLalla, V., Jr., Epstein, M. A. and Hoffman, M. A.: Clinical Ballistocardiography, New York, MacMillan, 1952.

[33] v. Wittern, W. W.: Force Ballistocardiography. Wright Field ADC, Tech. Rep. #52-340, Nov., 1952, p. 31.

[34] Griswold, H. E., Jr., and Cunningham, D. M.: Federation Proc. **14:** 64, 1955.

[35] Smith, J. E. and Rosenbaum, R.: Studies of the second degree of freedom in ballistocardiography. Am. Heart J. **46:** 799, 1953.

[36] Braunstein, J., Oelker, C. E. and Gowdy, R. C.: Design of a two-dimensional ballistocardiograph. J. Clin. Invest. **29:** 1219, 1950.

[37] v. Wittern, W. W.: Unpublished calculations.

[38] Rappaport, M. B., Sprague, H. B. and Thompson, W. B.: Ballistocardiography: I. Physical consideration. Circulation **7:** 229, 1953.

[39] Pordy, L., Chesky, K., Master, A. M., Taymor, R. C. and Moser, M.: The dual displacement and velocity ballistocardiograph apparatus. Am. Heart J. **44:** 311, 1952.

[40] Arbeit, S. R.: Personal communication, 1954.

[41] Harrison, T. R.: Symposium on BCG. Second International Congress of Cardiology, Washington, Sept. 1954.

[42] Dock, W.: Symposium on BCG. United States Public Health Service, Atlantic City, N. J., May 1954.

[43] Edson, J. N., Flamm, G. H., Dickes, R., Tobin, M. and Loeb, L. Thoracic ballistocardiography. Am. Heart J. **48:** 897, 1954.

[44] Starr, I., Schnabel, T. G., Jr. and Maycock, R. L.: Studies made by simulating systole at necropsy. Circulation **8:** 1, 1953.

[45] Ernsthausen, W., v. Wittern, W. W. and Reissman, R.: The Torsion Ballistocardiograph. U. S. Air Materiel Comm. Rep. MCRED-696-116A, Randolph Field, 1948.

[46] Scarborough, W. R., Beser, J., Talbot, S. A., Mason, R. E., Singewald, M. L. and Baker, B. M., Jr.: A method for recording ballistocardiographic vectors. Bull. Johns Hopkins Hosp. **87:** 235, 1950.

[47] Terry, F. M.: Electricity and Magnetism. New York, McGraw-Hill, 1929, p. 25.

[48] Taylor, H. L., Maloney, W. F., and Keys, A.: Factors affecting the low-frequency, critically-damped ballistocardiogram, with special reference to age, body size and body composition, Am. Heart J. **48:** 864, 1954.

[49] Starr, I.: On various types of ballistocardiographs and on the methods of standardizing them. First International Congress of Cardiology, Paris, 1950.

[50] Burger, H. C.: Ballistocardiography. In press.

[51] Talbot, S. A.: Unpublished Symposium on BCG. United States Public Health Service, Atlantic City, N. J., May 1954.

[52] Warburg, E.: A method of determining the undamped natural frequency and the damping in heavily damped systems. Acta physiol. scandinav. **19:** 344, 1949.

[53] Tobin, M., Edson, J. M., Dickes, R., Flamm, G. H., Deutsch, L.: The elimination of body resonance distortion from the direct-body ballistocardiogram. Circulation **12:** 108, 1955.

Appendix 7.

Transmission spectrum and system-frequencies of a damped body-bed system. The equations of a damped two-mass system may be solved quite briefly: For a single frequency f, the force equations (2a) become in vector form[42]:

$$(2a) \quad -\omega^2 y_b + j\omega \frac{r_b}{m_b}(y_b - y_p) + \frac{k_b}{m_b}(y_b - y_p) = \frac{F_b}{m_b}$$

$$(2b) \quad y\left(-\omega^2 + \frac{k_p}{m_p} + \frac{j\omega r_p}{m_p}\right) + \frac{k_t}{m_b}(y_p - y_b) + j\omega \frac{r_b}{m_p}(y_p - y_b) = \frac{F_p}{m_p},$$

Change into dimensionless form by substituting the ratios below:

$$\frac{r_b}{m_b} = \rho \qquad \frac{m_b}{m_p} = \mu$$

$$\frac{r_b}{m_p} = \mu\rho \qquad \frac{r_p}{r_b} = R$$

$$\frac{r_p}{m_p} = \mu R\rho \qquad \frac{f_p}{f_b} = F$$

$$\frac{k_b}{m_b} = \omega_b^2 = 4\pi^2 f_b^2 \qquad \beta = \frac{\omega}{\omega_b} = \frac{f}{f_b}$$

$$\frac{k_b}{m_p} = \omega_b^2\mu \qquad Q = \frac{m_b\omega_b}{r_b} = \frac{\omega_b}{\rho}$$

$$\frac{k_p}{m_p} = \omega_p^2 = \omega_b^2 F^2 \qquad \beta' = \beta/Q$$

and divide by ω_b^2:

$$\text{(3a)} \quad y_b(1 - \beta^2 + j\beta') - y_p(1 + j\beta') = \frac{F_b}{m_b\omega_b^2}$$

$$\text{(3b)} \quad y_p[F^2 + \mu - \beta^2 + j\beta'\mu(1 + R)] - y_b(\mu + j\beta'\mu) = \frac{F_p}{m_b\omega_b^2}$$

From this pair of equations, the various ballistocardiograph frequency characteristics can be derived in a single algebraic step, as follows:

IA. To get the spectrum of *platform displacement* referred to *force driving the platform*, set $F_b = 0$ and eliminate y_b:

letting $A = 1 + \mu + F^2 + R\mu/Q^2$

$$B = \mu R + F^2$$

$$C = 1 + \mu + \mu R$$

$$\text{(4a)} \qquad \frac{y_p}{F_p} = \frac{\mu}{k_b}\frac{(1 - \beta^2) + j\beta/Q}{D}$$

where $D = (F^2 - A\beta^2 + \beta^4) + j\beta(B - \beta^2 C)/Q$.

This is the equation shown graphically in figure 2*C* the dotted line.

B. To get the spectrum of *platform acceleration* referred to *force driving* the platform, multiply (4a) by ω^2 and use the relation $\mu/k_b = \beta^2/m_p\omega^2$

$$\text{(4b)} \qquad \frac{\omega^2 y_p}{F_p} = \frac{\ddot{y}_p}{F_p} = \frac{\beta^2}{m_p}\frac{(1 - \beta^2) + j\beta/Q}{D}$$

These solutions are left in the form of vector components, as more useful for comparison and checking. The expressions for amplitude and phase are readily derived by vector algebra. Thus for the general form $\frac{u + jv}{w + jz}$, appearing in equation (4): the in-phase component is $\frac{uw + va}{w^2 + z^2}$; the quadrature component is $\frac{v(w - v)}{w^2 + z^2}$; the phase angle $\tan^{-1}\phi$ is $\frac{v(w - z)}{uw + vz}$; the amplitude is $\sqrt{\frac{w^2 + v^2}{w^2 + z^2}}$. These algebraic forms are too cumbersome to be informative. Instead, we have presented the same results in graphic form (figs. 3 and 4). The solutions were obtained by reading voltages from an electric analog, a circuit having identical equations (fig. 2*C*).

II A. To get the spectrum of *platform displacement* referred to *force on body*, set $F_p = 0$ and eliminate y_b from equations 3:

$$\text{(5a)} \qquad \frac{y_p}{F_b} = \frac{\mu}{k_b}\frac{1 + j\beta/Q}{D}$$

This is the behavior of a two-mass mechanical filter at first flat, then falling off at the rate of f^2 and eventually at f^3. It is the response characteristic of the Starr or Nickerson ballistocardiographic methods (fig. 3*A*), using corresponding values of platform stiffness and damping.

B. To get the spectrum of *platform acceleration* referred to *force on* body, multiply this by ω^2:

$$\text{(5b)} \qquad \frac{\omega^2 y_p}{F_b} = \frac{\ddot{y}_p}{F_b} = \frac{\beta^2}{m_p}\frac{1 + j\beta/Q}{D}$$

Since the quadrature component (j terms) is small ($Q = 2$) in mid-spectrum, the acceleration characteristic is flat in the middle, and drops at both ends (fig. 3*B* and 4*B*): fast at low frequency ($\beta \ll 1$) as shown by the F term, and slowly at high frequency (fig. 7). This is the behavior of a *bandpass* mechanical filter, which is the nature of the low frequency ballistocardiograph suspensions which record acceleration. It is the same as equation (5a) but rotated clockwise about f_b (as in fig. 1*C*).

III. To get the locus of the two *system frequencies* for the free oscillation of a *damped* two mass system, make both F_b and $F_p = 0$, eliminate y_b and y_p simultaneously from equation 3a and 3b and solve for $\beta \equiv f/f_b$:

$$\text{(6a)} \quad (\beta^4 - A\beta^2 + F^2) + j\beta(B - \beta^2 C)/Q = 0$$

i.e., real part + imaginary part = 0

recognizable as the denominator D of equation (4) and 5.

Since this whole vector equals zero, its "real part" does also. This yields the formula for the natural modes of oscillation of the doubly damped two-mass system, i. e., the two system frequencies:

$$\text{(6b)} \quad \beta_{1,2}^2 = f_{1,2}^2/f_b^2 = A \pm \sqrt{A^2 - 4F^2},$$

where, as before

$$A = 1 + \mu + F^2 + \mu R/Q^2$$

$$F = f_p/f_b$$

Without damping ($\mu R/Q_b^2 = 0$), $A = 1 + \mu + F^2$ and (6b) reduces to:

$$(7)\quad f_{1,2}^2 = f_b^2/2[M + F^2 \pm \sqrt{(M + F^2)^2 - 4F^2}]$$

where $M = 1 + \mu = \dfrac{m_b + m_p}{m_p}$

This is the equation for $f_{1,2}$ derived in appendix 8 for an *undamped* system, and plotted in figure 6. The effect of the damping shown in equation 6b is to *shift* the line of symmetry in figure 6 to slightly *higher* frequencies, by the damping term $\mu R/Q^2 = \dfrac{r_p r_b}{m_p k_b}$ determined by mass of platform, spring and damping of body. It also *spreads* the lines of Figure 6 by a similar value. With actual ballistocardiograph values, the error of the curves in figure 6 due to neglect of damping is about two per cent.

Appendix 8

The two undamped *system frequencies* or natural resonant modes of the body and bed coupled together are obtained more simply, by substituting the vector (appendix 2) in equation (3) above and equating to zero F_p, F_b and the damping. From this "homogeneous equation" the y's drop out, and the resulting simple quadratic equation relates the system frequencies $f_{1,2}^2$ ($= \omega_{1,2}^2/4\pi^2$) to the frequencies of body alone (f_b) and platform alone (f_p):

$$f^4 - f^2\left[f_p^2 + \frac{m_b + m_p}{m_p} f_b^2\right] + f_b^2 f_b^2 = 0.$$

Solving this for $f_{1,2}^2$:

$$(7)\quad f_{1,2}^2 = f_b^2/2\left[f_p^2/f_b^2 + \frac{m_b + m_p}{m_p} \pm \sqrt{\left(f_p^2/f_b^2 + \frac{m_b + m_p}{m_p}\right)^2 - 4f_p^2/f_b^2}\right]$$

which is identical with equation (7) above. These two values of f^2 give the two branches of the curve in figure 6, plotted as frequency *versus* platform stiffness, k_p, with mass, m_p, as parameter, by substituting: $f_b = 5$ *c/s*, $m_b = 150/384$ and $f_p^2 = k_p/4\pi^2 m_p$. These system-frequency lines also mark the theoretical "corner" or low- and high-cut frequencies for the ballistocardiograph spectrum band, *for all possible values of masses and springs of the body and platform.*

(a) In particular, for platform springs much *stiffer* than body springs (upper half of figure 6) and light platforms, the curves *approach* straight lines (asymptotes) whose values are:

$$\textit{lower system frequency } f_1 = f_p\sqrt{\frac{k_p}{k_p + k_b}} = f_b(1 - k_b/2k_p) \leq f_b$$

which is just under the body natural frequency, or the body oscillating on both springs in series.

$$\textit{upper system frequency } f_2 = \frac{1}{2\pi}\sqrt{\frac{k_p + k_b}{m_p}} \geq f_p$$

which is just over the platform natural frequency, or the platform oscillating between body and earth.

(b) For platform springs much *softer* than body springs (lower half of figure 6), the asymptotic lines are:

$$\textit{lower system frequency: } f_1 = f_p\sqrt{\frac{m_p}{m_p + m_b}},$$

$$\text{or}\quad f_1 = \frac{1}{2\pi}\sqrt{\frac{k_p}{m_p + m_b}} \leq \frac{1}{2\pi}\sqrt{\frac{k_p}{m_b}}$$

which is just under the frequency of body mass oscillating on platform stiffness;

$$\textit{upper system frequency: } f_2 = f_b\sqrt{\frac{m_p + m_b}{m_p}}$$

$$\text{or}\quad \frac{1}{2\pi}\sqrt{\frac{k_b}{m_t}\cdot\frac{m_b + m_p}{m_p}} \geq \frac{1}{2\pi}\sqrt{\frac{k_b}{m_p}}$$

which is just over the frequency of platform mass oscillating on body stiffness.

Appendix 9.

Nickerson's transfer function method[25] was used to illustrate a way of removing bed-distortions by the inverse operation. One multiplies the *transmission* spectrum of the body (f_p/f_b plotted vs. frequency) by the *response* spectrum of the platform as a second oscillator (y_p/f_p); the product gives the overall transfer relation of the combination (y_p/f_b). This approach avoids complex algebra or analog computers in finding the interaction of two damped oscillators; though it employs the same mechanical assumptions.

The method proposed does illustrate clearly the effects of supports on the ballistocardiograph record. It is a good approximation for the Starr

method where little velocity transfers to the bed, though the outcome differs somewhat from ours. In this approximate method,[25] combining the responses moves the resonances *together*; in the exact method used in part II, the interaction moves them *apart*. That is, the Starr-bed resonance frequency falls *below* that of body alone (with footboard). When applied to the Nickerson bed above 4 cycles per second, where the platform moves relatively to the body (motional impedance small) the approximate method[25] is rather less accurate. The "overall" transfer function then differs considerably from the product of the two components.[14] It results that the cardiovascular "force" spectra[25] determined and compared for the different beds by using this method inversely, need recalculation above body frequency. In general, the physical chain (heart-skeleton-muscle-bed) cannot be so resolved into successively multiplied components (as proposed also by v. Wittern for the internal segments), without knowing in detail about the energy transfer. The less compact method used in this paper does include transfer of coupling energy from body to platform.

Motion in Cardiovascular Radiography

By CHARLES T. DOTTER, M.D.

The minute has given way to the second as an expression of radiographic exposure duration. It is predicted that the millisecond will be the term of the future. Arterial blood velocity exceeds 50 cm. per second. In cardiovascular radiography, especially angiocardiography, maximum detail cannot be achieved unless the x-ray exposure is short enough to "stop" rapid movement. Practical experience indicates that exposures of 3 milliseconds' duration offer an economic alternative to high speed, serial angiocardiography. A method of achieving such exposures consists of a grid-controlled, high-tension, switch tube operated in series with the diagnostic x-ray tube.

MOTION affects the study of all living patients and, since 1896, has been of special concern to those dealing with x-rays. Economically, its importance is obvious. Undesired patient-movement during radiographic exposures impairs detail and, thereby, necessitates repeat examinations if mistakes are to be avoided and maximum diagnostic yield obtained.* More fundamental ways in which motion plays a role are illustrated by three overlapping, radiologic approaches to the study of the heart. *The chest film* by a single exposure minimizes (but does not "stop") motion. *Angiocardiography*, through serial radiographs, though not directly studying motion, makes use of its effects. *Cinefluorographic angiocardiography* constitutes a primarily dynamic approach, the study of motion itself being dominant.

In the ensuing discussion, various direct radiographic technics for angiocardiography will be contrasted as to their usefulness and limitations. Following this, an attempt will be made to define a practical basis for clinical angiocardiography in terms of frequency and duration of x-ray exposures. It is believed that considerable confusion exists in this matter and that a logical approach is desirable. A relevant technical development will be described which allows radiographic exposures of unusually short duration.

Exposure Rates for Conventional Serial Angiocardiography

Clinical angiocardiography is usually accomplished by direct serial radiography following the injection and many different devices exist which provide the necessary rapid film-shifting.[1] Controversy exists, concerning the number of exposures per second desirable for angiocardiography. The optimal rate can be assumed to be some place between advocated extremes of 1 and 12 per second. If new and better equipment is to become available, more precise specifications are needed. Advice given to the manufacturers should be carefully considered. The enthusiastic desire, to incorporate many extra, nonessential features in a new piece of equipment, can result in failure from the point of view of design, manufacture, sales, operation, maintenance and cost. Money and engineering spent in development and fabrication of useless refinements could far better be directed elsewhere. Thus it is advisable to explore in a logical manner certain factors bearing upon exposure rates for angiocardiography. These factors are:

(1) *The period of study should be that of the transit period of the bolus of contrast agent.* For practical purposes, in the absence of heart failure, this amounts to the 10 seconds following the injection. Films made thereafter will be worthless.

(2) The exposure rate determines to a variable extent the amount of radiation involved. It determines to a great extent the cost of a given examina-

This study was aided by the Machlett Laboratories, Inc. and the Mallinckrodt Chemical Works.

From the Department of Radiology, University of Oregon Medical School, Hospitals and Clinics, Portland, Ore.

* Painridden patients, frightened children, and inferiorly-trained technicians all contribute to the costly total of re-examinations necessitated by movement during exposure. At the University of Oregon Medical School, about 0.5 per cent of the film exposed is so wasted. It is estimated that undesired motion costs U. S. radiologists as much as $250,000 a year.

tion and, to an even more serious degree, the magnitude of equipment-design problems and costs. Thus, *the optimal rate* (and similarly the film size) *is the minimum needed to produce the desired clinical result.*

(3) Adequate *detail should be achieved through short exposures* rather than the "hit or miss" technic of making many films in hope that one of these will be made during a period of immobility and will, therefore, be adequate. This point will be more fully discussed subsequently. To repeat, the search for detail should not influence the exposure rate.

(4) *The exposure rate (number of films per second) needed to show all the visualizable cardiovascular structures can readily be calculated.* Disregarding "unsharpness" due to movement during exposure, this depends upon the length of time during which there will be diagnostically adequate concentration of the contrast agent at any given point in its route through the heart and great blood vessels. The duration of injection represents the minimal "spot opacification" period since the bolus tends to "string-out" during its passage. Study of the pulmonary valves serves to illustrate this point. Following angiocardiographic injection, there occurs excellent opacification of the pulmonary outflow tract (pulmonary conus and pulmonary artery) for a period of at least two seconds duration. If at any instant during this period, an exposure is made in the correct projection, the rays will pass through the pulmonary valves while the leaflets are in contact with adequate concentrations of contrast agent. *Thus an exposure rate of one per second is theoretically adequate to show any structure which might be revealed in studies made at far higher rates.* Doubling this rate to two per second and controlling the time of exposure electrocardiographically will theoretically afford visualization of all structures during the extremes of their systolic and diastolic excursions.*

(5) The specific clinical fact sought for often requires that less than two films per second be made. Superior vena caval block (an extreme example) is as well shown by four films during 10 seconds as by 44. Two-per-second exposure rates will suffice for investigative purposes where systolic and diastolic extremes are desired; higher rates would be desirable for studying intervening phases. Since there is good evidence that clinical angiocardiography need not be concerned with cyclic extremes (let alone intermediate phases), manufacturers would be designwise to relegate such problems to the area of special research devices.

The foregoing discussion leads to the conclusion that adequate diagnostic angiocardiography requires two or at most four exposures per second. Reasoning has been based upon the relatively slow movement of a bolus of radiopaque solution. Thus far, consideration has not been given to movement of the heart itself. *The duration, as well as the frequency, of exposures is of great importance.*

Exposure Duration in Angiocardiography

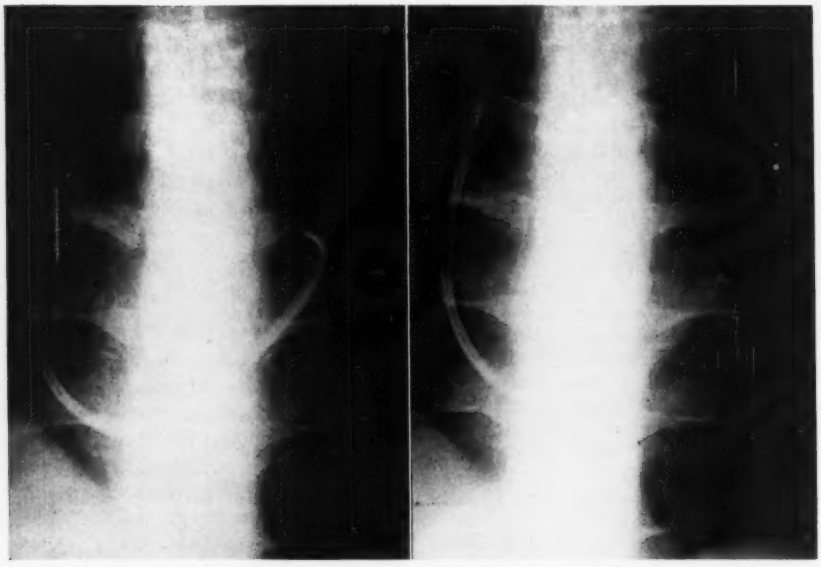
Many workers, with wide experience in angiocardiography, have strongly expressed their desire for angiocardiographic exposure rates in excess of two or four per second. Lind and Wegelius[2] and Kjellberg[3] are currently employing exposure rates of up to 12 per second. Justification for this expensive practice (film for a 10-second run in one projection might cost as much as $100.) has been their belief that slow, serial studies are inadequate for many clinical states, especially left to right and bi-directional congenital cardiovascular shunts. This report is being written in support of a more efficient, alternative approach.†

A moderately odious analogy may be appropriate: To shoot a rabbit, the wise hunter, by choice, and the impoverished one, by necessity, are prone to accomplish their objective through a single, well-aimed, rifle bullet. An equally lethal alternative might be to fire a submachine gun in the general direction of the rabbit at an explosion rate of 12 per second. The rapid rate involves a greater expenditure of ammunition, a more expensive gun, increased "wear and tear" on hunter, quarry, and countryside as well as much more noise. The essential feature of the more economic method lies in the aim. It is here contended that adequate radiographic detail represents the "aim" of the above analogy.

The unusual success of Swedish workers in

* Systolic-diastolic studies can be achieved without electrocardiographic control by much higher exposure rates and attendant gross inefficiency. Experience indicates that the ends of clinical diagnosis do not justify the means (whether electrocardiographic exposure control or rapid serial exposure rates).

† These remarks do not apply to the elaborate, highly-revealing investigations of cardiac physiology as exemplified by Lind and Wegelius' contributions to the understanding of fetal and neonatal circulation. Such studies, of necessity, take into consideration the various stages of cardiac contraction and represent a highly-informative, investigative approach.



A B

FIG. 1. *Cardiac Movement.* *A* and *B* are spot films of a cardiac catheter the tip of which lies in the pulmonary outflow tract. Though exposures were made in rapid succession and at technically identical factors (1/20 second), the tip of the catheter is invisible in *B* due to cardiac motion during this exposure.

showing pulmonary valvular detail is disproportionately greater than can be accounted for by the numerical increase in the number of exposures per second. It follows that a factor, other than the exposure rate itself, is involved. This factor is *exposure duration.* Workers, employing high-exposure frequency technics, have of necessity utilized high energy generators and short exposures. Kjellberg uses $\frac{1}{250}$ a second during angiocardiography at 12 exposures per second. Most studies performed in our country make use of exposures lasting $\frac{1}{60}$ second or longer (often as long as one-tenth of a second). It is this significantly long exposure (rather than the number of films made) which defines the limits of conventional angiocardiographic technic in the United States.

While the optimal angiocardiographic exposure frequency is determined by rate of progress of the bolus itself, the duration of exposure is dependent upon the rate of movement of parts of the bolus and by the movement of any anatomical structure coming into contact with it. In the venous system, mean blood

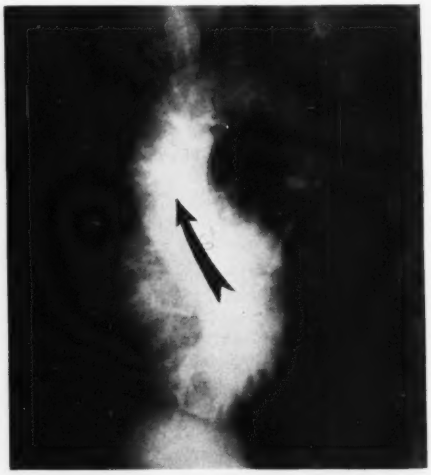


FIG. 2. *Blood velocity.* The movement of blood which occurred during this angiocardiographic exposure (made during ventricular systole at $\frac{1}{20}$ second exposure duration) is represented by the superimposed arrow drawn to scale. Such a technic cannot be expected to reveal heart valves or trabecular detail unless made at a certain (elusive) moment during diastole.

FIG. 3. *Effective "frozen motion" through strobe photography.* The ultra short exposure ($\frac{1}{5000}$ second) reveals information that could not have been obtained by conventional photography, through movies or on direct observation. Ultra short exposures offer a radiographic analogy applicable to the cardiovascular system.

velocity is approximately 4 to 10 cm. per second; in both the aorta and pulmonary artery, physiologists indicate that resting mean arterial blood velocity ranges between 50 and 100 cm. per second! During systole, movement of the pulmonary and aortic valves will reflect this high velocity (see figs. 1 and 2). If adequate definition of these valve leaflets requires that they be "stopped" radiographically during an excursion equal to $\frac{1}{10}$ their assumed thickness of 1 mm., it follows that the exposure *of the film* must be approximately $\frac{1}{5000}$ of a second. Fortunately, for clinical cardiovascular radiology, such ultrashort exposures are unnecessary. Exposures $\frac{1}{500}$ of a second (two milliseconds) should suffice for practical purposes.* In providing detail sufficient to the need, such short exposures offer a highly economical alternative to rapid exposure studies in angiocardiography. Judged on the basis of preliminary studies, ultrashort exposures give anatomical information hitherto not available regardless of the exposure frequency employed. Analogously, ultrashort exposure "strobe" photography often provides information not discernable in ordinary photographs, through movies, or on direct observation (fig. 3).

* Probably because semilunar valve movement occurs at much lower speeds than published arterial flow velocities.

Half-Wave Rectification

Most modern heavy-duty diagnostic radiographic equipment affords exposures as short as $\frac{1}{60}$ of a second, i.e. two rectified impulses Occasionally, it may be possible, by temporarily decommissioning two valve tubes, to achieve half-cycle exposures. This deliberate sabotage reduces by substantially more than half the duration of film exposure. The useful exposure period in the conventional $\frac{1}{60}$ second (two impulses) exposure is actually about $\frac{1}{80}$ second, while a single impulse will produce a (measured) effective exposure of only $\frac{1}{240}$ second! The three-fold gain is readily understandable since, as a result of filtration, x-rays generated during the initial and terminal phases of a given impulse fail to reach the film at all. This accounts for the fact that $\frac{1}{60}$ second on the control panel may mean $\frac{1}{80}$ second at the film. Through elimination of the "silent" period between the effective portion of succeeding impulses, the three-fold shortening of exposure length is explained. This technic offers a proved, worthwhile improvement in the quality of angiocardiograms which can be achieved without great expense. Advice concerning the feasibility of such a change should be obtained from the manufacturer's technical service division.

High-kilovoltage radiology is becoming commonplace and still further shortening of exposures is therefore possible. This cannot be done by filtering the beam without inordinate loading of diagnostic tubes.

High Tension Switch-Tubes for Diagnostic Roentgenology

A striking demonstration of short exposures in radiography is offered by technics employing surge generators and electron arc cathodes. Utilizing condenser discharges, Slack and coworkers[4] produced extremely brief x-ray exposures of tremendous energy (fig. 4). Unfortunately, such a technic cannot make use of commonly available diagnostic equipment.

In an effort to secure greater angiocardiographic detail through short exposures, assistance was sought from the Machlett Laboratories. Consultations with Mr. H. S. Cooke and

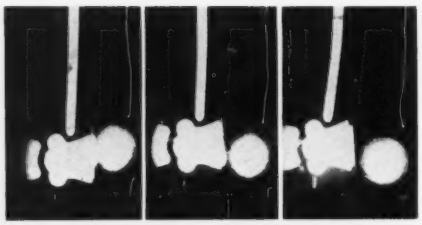


FIG. 4. *Ultra short radiographic exposures* (one microsecond in duration) showing the impact of golf club and ball. Available through the kindness of Dr. Charles M. Slack, Westinghouse Corporation.

Mr. W. E. Stevenson and Mr. T. H. Rogers led to the conclusion that, of the possibilities considered, a grid-controlled, electron tube operated in series with the diagnostic x-ray tube offered the most profitable approach. An experimental tube, constructed by Machlett, proved capable of providing three millisecond exposures at diagnostic energy levels. The description of the tube follows.

The tube, a triode, consists of filament (cathode), plate (anode), and intervening grid, the elements being contained within an evacuated glass envelope (fig. 5). The energized switch-tube filament serves as a source of electrons. The tube has a "cut off" point at −250 volts on the grid with +125 kilovolts on the anode. Thus, even though the primary circuit of the high tension transformer is completed, electrons are unable to reach the anode since except during exposures they are repelled by a negative charge (−300 volts) on the grid. Current therefore does not flow in the high tension circuit. The exposure is made by electronically altering the grid voltage or bias from −300 to +300 volts. At this positive grid charge, the tube will pass approximately 700 milliampere peak with less than 500 volts drop to the anode. As long as the grid is held at its positive charge, current flows through the tube completing the high tension circuit.

The desired grid bias voltages are readily obtained and applied to the switch-tube electronically (in this case by using an electronically timed "flip-flop" circuit isolated from ground by a transformer insulated for 60 kilovolts). It is thus possible to determine precisely the duration of the positive bias, and therefore the length of the exposure. The change in grid potential which causes the switch-tube to conduct may be likened to a flimsy key unleashing the tremendous force of the exposure current. Due to the relatively low grid current, electronic circuits suffice. Phasing of the exposure pulse with relation to the utilized sine-wave impulse may be varied readily. Thus, control of quality of the beam can be achieved independent of the high tension transformer. This may prove to be of importance in equipment design. At the high kilovoltages and short exposures employed, the beam is composed of fairly uniformly penetrating rays. Thus far, loss of contrast has not proved to be a factor of importance. Diagnostic applications of the fairly homogeneous x-rays beams which can be obtained by this tube are being explored.

On Nov. 23 and 24, 1954, preliminary appraisals of short exposure technics, utilizing this tube, were conducted by the author and Machlett engineers at the Machlett Laboratories in Springdale, Conn. Studies consisted of radiographic examination of the anesthetized dog's heart during catheter injection into the superior vena cava of 10 to 15 cc. of Urokon sodium, 70 per cent. Factors which proved satisfactory for one of the animals were 750 milliampere peak (equivalent to conventional 500 milliamperes), 95 kilovolt peak (KVP), 3 msec. ($\frac{1}{333}$ second) and a distance of 36 inches between the 2 mm. focal spot and the film. The dog's chest measured 18 cm. in the projection employed; while Eastman Bluebrand film and Patterson parspeed intensifying screens were used. Numerous radiographs at varying factors were made. The results, believed to be highly encouraging, are exemplified by figure 6.

Detail was greatly improved. As a result, visualization was far superior to that of controls exposed at $\frac{1}{10}$ second. Trabeculae carnae within the right auricular appendage and ventricular trabecular muscles were distinctly revealed. Hitherto invisible minimal retrograde reflux of contrast solution entered tributaries of the superior vena cava. When this did not occur, contributory or mixing "jets" were routinely present and revealed the site and relative volume of streams of nonopaque blood-deforming contrast substance within the

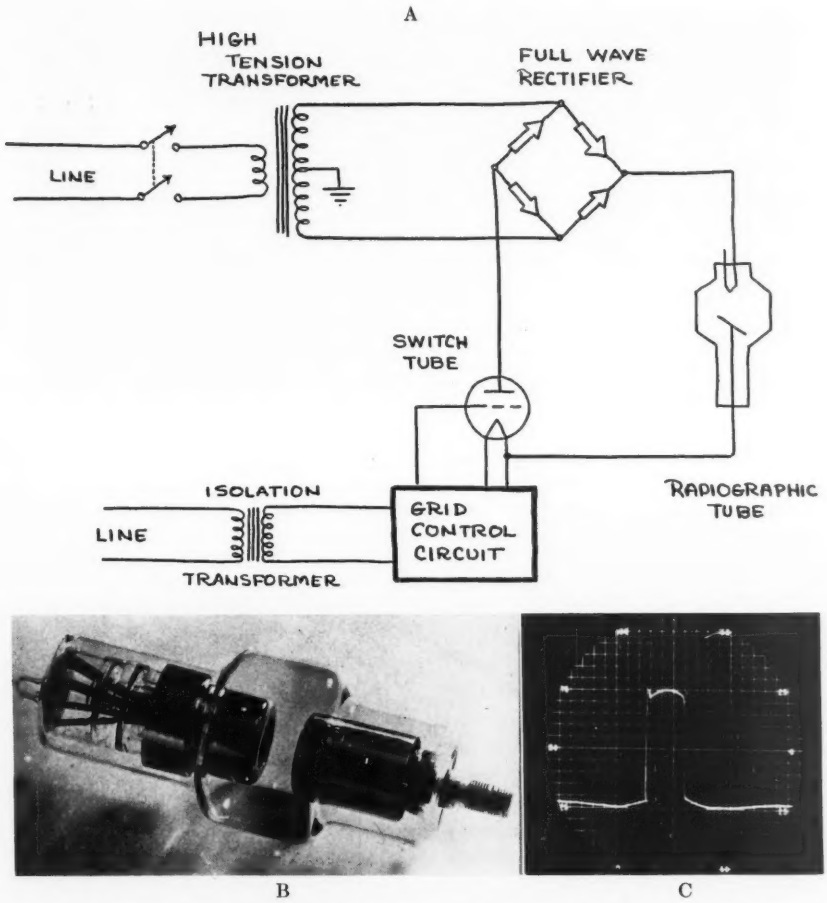
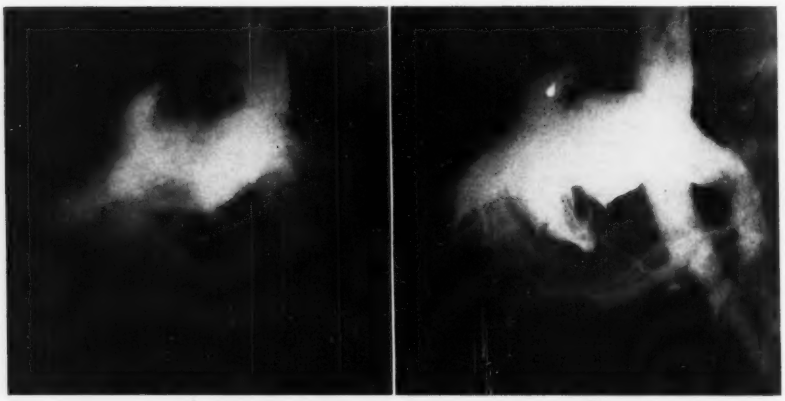


FIG. 5. *High Tension Switching Triode for Diagnostic Radiography. A.* Circuit diagram. Electronically changing the grid voltage in the switch tube, *B* shows a "low power" operation allowing the high-powered, much higher voltage of the x-ray generator to create a current through the switch tube and the x-ray tube, *C* shows an oscilloscopic photograph of a 3 msec. x-ray tube pulse so controlled. With conventional technics, x-ray exposures are longer and less efficient.

superior vena cava and right atrium. Clarification of the border between blood and contrast substance was sharp, allowing a fairly precise definition of the extent of the bolus. Demonstration of the leaflets of the tricuspid valve was unmistakable. Though during these preliminary tests but one exposure could be made following a given injection, more information was gained about the right side of the heart and its tributaries than would probably have been obtained from the first four exposures of a conventional two-films-per-second serial study. Thus, the added detail achieved through short exposure duration reduces the need for high exposure frequencies and simplifies the problem of equipment design accordingly. It is probable that through short exposures, the volume of angiocardiographic injection can be reduced, thus increasing the safety of angiocardiography (while at the same time its diagnostic potential is enhanced).

A switch-tube has been installed in one of the regular radiographic rooms of the Department of Radiology of the University of Oregon



A B

FIG. 6. *Angiocardiography using a 3 Millisecond Exposure. Anesthetized Dog. A.* Control. Right heart opacified. Factors: 1/10 second exposure, 95 KVP, 12 milliamperes (RMS). *B.* Factors: 3 msec. exposure, 95 KVP, 750 milliamperes (peak). Detail is vastly improved. Tricuspid valve, atrial trabeculae, and contributory "jets" (see text) are revealed only in *B*. Such a technic increases the information gained from angiocardiography while reducing the amount of contrast agent needed (and thus possibly making the procedure safer).

Medical School. Installation caused few problems; routine use of the room is still possible since the tube itself is housed in a fairly small box and placed in the diagnostic room while the control box, even smaller in size, is placed as desired. Details of installation will vary according to the design of the equipment being modified. Basically, an important objective is realized in that the switch-tube timer-contactor is readily adapted to ordinary diagnostic apparatus and does not preclude the use of a more conventional timer. Since there is reason to believe that the life expectancy of the tube will be good and the production cost need not be prohibitively high, the switch-tube should not be relegated to the limbo of "for research only."

Short exposure technics represent a logical step in the progress of diagnostic radiology. As high kilovoltage through "wide latitude" technics can decrease film wastage due to improper quantitation of exposures, so can "short shot" technics minimize the effect of unwanted motion during radiography. Since at 120 kilovolt peak (KVP) an adequate chest film of the average adult requires less than 1 milliampere-second, ordinary high voltage diagnostic tubes and generators will suffice. It is

FIG. 7. *A non watery opaque substance.* When safe particulate agents (not necessarily solid but capable of producing punctate areas of radiopacity) are achieved, there will result a tremendous expansion of the applications of angiocardiography to the fundamental and clinical investigation of the cardiovascular system. Very short, precisely timed x-ray exposures will be essential.

predicted that short-duration exposures will expand the potentialities of angiocardiography to a considerable extent. The definitive diagnosis of septal defects with left-to-right blood-shunting may eventually fall to the radiologist rather than to those employing cardiac catheterization. Its applications in the study of ventricular

form and function are unexplored. Preliminary radiographic studies employing relatively short exposures in the study of the left ventricular wall in coronary heart disease are already in progress and should be enhanced by millisecond exposure technics. Calcified valves can be seen more clearly in radiographs made at short exposures than by fluoroscopy. Other applications such as in pediatric radiography are obvious.

A strong impetus toward the development of ultra-short exposure technics suitable for clinical applications has been a long-term interest in the development of satisfactory and harmless "particulate" contrast agents for use in cardiovascular roentgenology. These are a practical possibility and open up yet another unexplored approach. "Punctate" or particulate radiopaque agents of proper size and viscosity (whether solid, liquid or gas) should provide a radiologic method for studying the characteristics of blood flow (fig. 7). Abnormal turbulence patterns may offer valuable data in many disease states, such as valvular deformities and cardiac arrhythmias. By measuring particle excursion during exposures of sufficiently short, known duration, blood velocity and flow may prove to be simultaneously quantitable in many parts of the cardiovascular system. For example, simultaneous blood-flows in the pulmonary artery and all its segmental branches could conceivably be calculated from a single radiograph, while the determination could be repeated at much shorter intervals than allowed by technics based upon the Fick principle. Studies with "particulate" contrast agents necessitate the use of short exposures of a precisely known duration based upon the velocity of bloodflow.

Summary

(1) The radiologic significance of cardiovascular motion has been the underlying basis for the foregoing report.

(2) The optimal exposure frequency for clinical angiocardiography has been considered in detail in a conscientious effort to guide those concerned with design and manufacture of future apparatus. A combination of economic, clinical, anatomic, and physiologic reasons have been advanced in support of exposure rates of from one to four per second.

(3) The value of short-duration roentgen exposures for angiocardiography has been discussed at length. Diagnostic accuracy is improved while economy is achieved in terms of the number of films needed and the amount of contrast agent to be used. The duration of exposures for angiocardiography should be based upon the velocity of blood-flow in man. The two millisecond exposure appears to represent a reasonable objective. The frequency of angiocardiographic exposures is, on the other hand, best determined in terms of progress rate of the entire bolus of contrast agent.

(4) Through the use of an electronically-controlled, grid-operated, electron tube in series with the diagnostic tube, three millisecond clinical radiographic exposures have been achieved. The tube is described and a number of its potential applications to medicine discussed.

Acknowledgments

Machlett Laboratories, Incorporated, designed and constructed the switch-tube. The personal cooperation of W. E. Stevenson, H. S. Cooke, T. H. Rogers, G. F. Bavor, and C. Kirka is gratefully acknowledged. Dr. Arnold H. Janzen of Yale University Medical School arranged for experimental animals used in testing the switch-tube. The Mallinckrodt Chemical Works was of financial assistance. Sincere thanks are due the many sales and technical representatives of various x-ray equipment manufacturers who in discussion have aided and encouraged the author.

Summario in Interlingua

Es discutite le problema del frequentia optimal de expositiones angiocardiographic in le practica clinic. Considerationes economic, clinic, anatomic, e physiologic es presentate in supporto del selection de un frequentia de inter 1 e 4 expositiones pro secunda.

Es discutite in detalio le valor de roentgenoexpositiones a breve durantia pro ob-

jectivos angiocardiographic. Le duration del exposition debe esser determinate in relation al velocitate del fluxo sanguinee.

Per medio de un tubo electronic in serie con le tubo diagnostic, expositiones radiographic de un duration de non plus que 3 millisecundas ha essite effectuate. Le tubo usate es describite. Un numero de su applicationes potential in le practica medical es discutite.

REFERENCES

[1] Dotter, C. T. and Steinberg, I.: Angiocardiography. Annals of Roentgenology, vol. 20, New York, Paul B. Hoeber Inc., 1951.

[2] Lind, J. and Wegelius, C.: The role of the exposure rate in angiocardiography. Acta. radiol **39:** 177, 1953.

[3] Kjellberg, S.: Personal communication.

[4] Slack, C. M., Thilo, E. R. and Zavales, C. T.: High speed x-rays. Electronics Industry **3**: 104, 1944.

The Effect of Large Intravenous Doses of Sodium Borate on the Human Myocardium as Reflected in the Electrocardiogram

By Hadley L. Conn, Jr., M.D., Berniece B. Antal, M.S. and Lee E. Farr, M.D.

Large intravenous doses of sodium borate, given to seven patients with brain tumors, caused development of temporary but consistent hypoxic-type abnormalities in the S-T segments and the T waves of the electrocardiogram. Correlation of these electrocardiographic changes with blood boron concentrations, determined up to 48 hours after boron injection, indicated that the changes were probably the result of damage by boron, present intracellularly in the myocardium. The intracellular concentrations which cause electrocardiographic abnormalities are considered to be of the order of 100 μg. per milliliter, similar to concentrations which have been shown to inhibit respiration in in vitro myocardial preparations.

THE use of boron in neutron capture therapy for glioblastoma multiforme[1] has stimulated renewed interest in the acute toxic effects of this element. The boron dosage employed, 2 to 3 Gm. given intravenously as borate, has been reported to cause toxic reactions.[2] Observations, from this department,[3] of the clinical effects of rapid intravenous borate administration have been published elsewhere. Circulatory depression and collapse are among the undesirable manifestations which we have seen and which have also been reported by others. We are not aware of published studies on the pathogenesis of this circulatory derangement or the direct in vivo cardiac effects of boron. The present report deals with electrocardiographic changes noted in patients, during and after neutron capture therapy, and relates these changes to effects on the myocardium of administered boron. While it has been our practice to endeavor to obtain electrocardiographic tracings on patients undergoing this procedure, it was not until this time that the procedure itself could be carried out in such a manner that satisfactory tracings could be obtained in the majority of instances.

From the Brookhaven National Laboratory, Long Island, N. Y.

This research was supported by the Atomic Energy Commission.

Dr. Conn is an Established Investigator of the American Heart Association.

Procedures

These observations were carried out on seven patients, during and after neutron irradiations. In each instance, immediately before thermal neutron exposure, the patients received a rapid intravenous injection of borax taking only 55 to 120 seconds for administration. The total dose of borax ranged from 18.6 to 27.3 Gm. (1.96 to 2.88 Gm. boron) which was equivalent to a range of 32 to 50 mg. of boron per kilogram of body weight.

Serial electrocardiograms were recorded on the Sanborn direct writing electrocardiographic recorder. Intermittent recordings, from the time of injection during the neutron capture therapy and up to about one hour afterwards, were made in all patients. In 6 of the 7 patients, additional records were obtained 24 to 48 hours after treatment. Standard limb leads were used in all recordings and the post-therapy tracings additionally included V leads.

Boron blood levels were determined on all seven patients after boron administration, at varying intervals from one minute to 48 hours. Estimation of boron concentration in whole blood was made by a modified quinalizarin method.[4]

Results

In all seven patients the electrocardiographic pattern was essentially the same during the first hour after the boron injection. For approximately five minutes after injection, no electrocardiographic abnormalities other than a modest increase in heart rate were observed. After the first 5 to 10 minutes, a frank sinus tachycardia always developed and cardiac rates of 100 to 160 per minute were usually present for several hours thereafter. More or

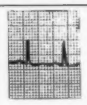
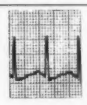
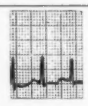
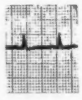
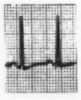
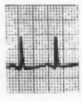
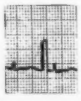
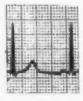
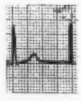
TIME AFTER INJECTION	BLOOD BORON CONCENTRATION	STANDARD LIMB LEADS I	II	III
3 MINUTES	189 μg./ml.			
25 MINUTES	78 μg./ml.			
24 HOURS	12 μg./ml.			
48 HOURS	2 μg./ml.			

FIG. 1. Electrocardiographic abnormalities occurring after an intravenous injection of borax. Mrs. D. R. 6408, aged 31, was given an intravenous injection of 22.1 Gm. of borax containing 2.3 Gm. of boron. Three minutes after the injection the Electrocardiogram remained normal when the blood boron concentration was 189 μg. per milliliter. At 25 minutes, the typical "ischemic or anoxic" type of ST-T changes (see text) and sinus tachycardia were present when the blood boron concentration was 78 μg. per ml. Twenty-four hours after injection the Electrocardiographic pattern showed only slight though definite improvement. Blood boron concentration had fallen to 12 μg. per ml. Forty-eight hours after injection, the Electrocardiogram was normal and the concentration of boron in the blood had become negligible, 2 μg. per ml.

less coincident with the onset of tachycardia, the previously isoelectric S-T segments began to show a slight negative depression and the T waves began to decline in amplitude. After 10 to 20 minutes a maximal S-T depression, varying from 1 to 3 mm., was observed along with T waves which were of minimal positive amplitude, isoelectric, or, more commonly, diphasic. These abnormalities persisted without appreciable change during the ensuing 30 minutes over which initial recordings were made. On the day following treatment the electrocardiogram was normal in three patients, G. T. 6351, R. T. 5984, and E. D. 5972. In three patients, M. F. 6024, M. H. 6012, and S. M. 6480, the abnormal electrocardiographic pattern was only slightly improved after 24 hours. At this time, the tracing was approaching normal in a fourth patient, D. R. 6408. After 48 hours, the electrocardiogram was normal in all but two patients, M. F. 6024, and S. M. 6480. The tracings on these two patients later returned to normal, but the date of return was not established. No appreciable hypotension was observed in any patient during the period of the electrocardiographic studies.

Figure 1, showing serial recordings of the limb leads, demonstrates in moderate degree the abnormalities uniformly observed and also the typical time sequence of development and regression of these abnormalities.

Blood boron estimations, carried out on these patients, permit certain correlations and diversities to be pointed out. One patient, R. T. 5984, who received two irradiations six weeks apart, and the lowest boron dose, 32 mg. per Kg., showed a return to a normal tracing within 24 hours. The other two patients whose tracing returned to normal in 24 hours, G. T. 6351 and E. D. 5972, had each received a boron dose of approximately 42 mg. per Kg. On the other hand, M. G. 6012, who received the same dose but who clinically was much more toxic (presumably as a result of boron administration),

had not regressed to a normal tracing within this 24-hour period, following either of the two treatments given six months apart. Patient I. R. 6408, whose tracing was approaching normal after 24 hours, had received a dose of boron of 46.5 mg. per Kg. Patients M. F. 6029 and J. M. 6480, whose electrocardiogram remained abnormal after 48 hours, had received boron doses of 34 mg. and 50 mg. per Kg., respectively. That the electrocardiographic abnormalities are not caused specifically by high blood boron concentrations is shown by the fact that the deviations did not occur during the first five minutes after injection, when the concentration ranged as high as 249 μg. per ml. in J. M. 6480, and was from 170 to 180 μg. per ml. in most of the other patients. Delayed excretion of boron was marked in patients M. F. 6029 and M. H. 6012, as evidenced by blood concentrations of <40 μg. per ml. and 12 μg. per ml., respectively, 24 hours post injection. The other patients, including J. M. 6480, showed blood concentrations at this time of 4 to 6 μg. per ml.

The onset of electrocardiographic changes was unrelated to the initiation of neutron bombardment of the tumor area and no characteristic changes were noted during the neutron radiation. In this study, the exposure area was 10 by 10 cm. and the thermal neutron flux was 3×10^9 neutrons per square centimeter per second. In the group of 10 patients treated earlier,[1] the exposure area was 5 by 10 cm. and the thermal neutron flux was 2×10^8 neutrons per square centimeter per second. The total neutron dose was much larger in the present group of patients but the type of electrocardiographic changes was identical in both groups.

Discussion

These data indicated that blood boron concentration, per se, was not the critical factor in initiating electrocardiographic changes, for the electrocardiograms showed a normal pattern during the first five minutes, following boron injection, when blood levels ranged up to 249 μg. per ml., with a median concentration of 185 μg. per ml. The onset of cardiac disturbances, reflected by the electrocardiograph, was at 10 to 20 minutes after injection, at a time when significant amounts of boron have presumably entered the cell water. Approximate calculations, from blood boron disappearance curves and volume distribution data in these patients, suggests that a large fraction of the boron is within the cells. Agreement is found from similar calculations on blood boron disappearance curves and volume distribution data in dogs[5] and mice,[6] subjected to a rapid intravenous injection of boron. The present data also suggest that the period required for regression to a normal electrocardiogram is not dependent solely on blood boron concentration, *vide* J. M. 6480. However, in all the other patients, regression of electrocardiograms to normal had occurred, when the blood boron concentration was below 12 μg. per milliliter. One other patient, M. F. 6029, showed a blood boron concentration of 40 μg. per ml. after 48 hours because of severe oliguria and he continued to exhibit electrocardiographic changes. Prolongation of electrocardiographic changes would thus appear to be the result of cellular damage, resulting from a significant concentration of boron acting over some period of time.

The nature and general extent of the electrocardiographic changes were consistent and characteristic, although they were nonspecific abnormalities of the ST-T segments. This type of change is similar to that found with hypoxia of the myocardium and has often been referred to as the hypoxic or ischemic type of pattern. However, there is doubt whether this pattern specifically connotes hypoxia, because it occurs under other circumstances in which no cell hypoxia has been demonstrated, such as alterations in electrolyte concentrations and distribution, particularly of sodium and potassium, and following digitalis administration. While we cannot exclude an intracellular electrolyte derangement as a consequence of flooding of the myocardial cell with boron, other experimental work, done in vitro on slices of mammalian myocardium, showed that concentrations of the order of 100 μg. per ml. of boron in the medium produced inhibition of respiration.[7] This is in the range of the concentrations present in the in vivo perfusion medium of the patients, i.e. the blood.

A consideration of all the data we have presently at hand suggests this as a working hypothesis: the entrance of boron into the myocardial cell in appreciable concentrations produces an injury resulting in cell hypoxia which is reflected by a characteristic abnormal ST-T pattern in the electrocardiogram. Additional data are obviously required to validate this concept.

Summary

Serial electrocardiograms were recorded in seven patients receiving boron intravenously as a part of the neutron-capture therapy of glioblastoma multiforme. A consistent hypoxic type of electrocardiographic abnormality, involving decrease in amplitude or actual negativity of the ST-T segments, was observed acutely. When the boron was rapidly excreted or the total dose was less than 50 mg. per kilogram body weight the electrocardiogram returned to normal within 24 to 48 hours. A tentative hypothesis is advanced regarding the mechanism of action of boron in the myocardium.

Summario in Interlingua

Le administration intravenose de large doses de borato de natrium a 7 patientes con tumores cerebral causava le disveloppamento temporari sed infallibile de anormalitates hypoxicoide in le segmento S-T e in le unda T del electrocardiogramma. Le investigation del correlation de iste alterationes electrocardiographic con le concentration de boro in le sanguine a periodos usque a 48 horas post le injection resultava in constatationes que indica que le alterationes mentionate es probabilemente le consequentia de damnos causate per le boro que es intracellularmente presente in le myocardio. Le concentrationes intracellular de boro capace a evocar anormalitates electrocardiographic es probabilemente presso a 100 μg pro millilitro. Assi il se tracta de un concentration del grado general que es demonstratemente capace a inhibir le respiration de preparatos in vitro de texito myocardial.

REFERENCES

[1] Farr, L. E., Sweet, W. H., Robertson, J. S., Foster, C. G., Locksley, H. B., Sutherland, D. L., Mendelsohn, M. L. and Stickley, E. E.: Neutron capture therapy with boron in the treatment of glioblastoma multiforme. Am. J. Roentgenol. **71:** 279, 1954.

[2] Pfeiffer, C. C. and Jenney, E. H.: Pharmacology of boric acid and boron compounds. Bull. Nat. Formulary Comm. **18:** 57, 1950.

[3] Locksley, H. B. and Farr, L. E.: The tolerance of large doses of sodium borate intravenously by patients receiving neutron capture therapy. In preparation.

[4] MacDougall, D. and Biggs, D.: Estimation of boron in plant tissue. Analytical Chem. **24:** 566, 1952.

[5] Easterday, O. D.: Personal communication.

[6] Locksley, H. B. and Sweet, W. H.: Tissue distribution of boron compounds in relation to neutron capture therapy of cancer. Proc. Soc. Exper. Biol. & Med. **86:** 56, 1954.

[7] Kisch, B.: Effects of boron compounds on tissue respiration. Biochem. Ztschr. **235:** 35, 1931.

Hemodynamic Changes Associated with Fluid Retention Induced in Noncardiac Subjects by Corticotropin (ACTH) and Cortisone; Comparison with the Hemodynamic Changes of Congestive Heart Failure

By Roy E. Albert, M.D., Warren W. Smith, M.D. and Ludwig W. Eichna, M.D.

This study proposed to determine whether marked fluid retention, induced by ACTH and cortisone, produces hemodynamic alterations similar to those of clinical congestive heart failure. Of 20 noncardiac subjects, four gained marked amounts of fluid, became edematous and three developed symptoms and signs consistent with congestive heart failure. The associated hemodynamic changes were similar to those of congestive heart failure in that the heart enlarged, "blood volume" increased and right heart and venous pressure rose, but differed in that cardiac ouput and A-V oxygen difference remained normal. It is suggested that the hemodynamic state associated with marked fluid retention is a noncardiac circulatory congestion which simulates congestive heart failure in several non-specific hemodynamic functions but differs in that primary cardiodynamic functions remain normal and the heart does not fail as a pump.

CONGESTIVE heart failure is characterized clinically by the presence of circulatory congestion in the vessels leading to either the right heart, the left heart or both; it is this congestion which gives rise to most of the symptoms and physical signs considered diagnostic of congestive heart failure. One of the hypotheses advanced to explain the genesis of this circulatory congestion holds that a primary failure to excrete salt and water leads to the retention of fluid in the vascular system, which in turn produces the characteristic congestion and manifestations of congestive heart failure.[1, 2, 3] In recent years, there has been increasing evidence that clinical manifestations similar to those observed in congestive heart failure may occur in association with fluid retention of noncardiac origin, for example, after daily intravenous infusions of serum albumin,[4] during the oliguria of acute glomerulonephritis,[5, 6] following excessive fluid intake in lower nephron nephrosis[7, 8, 9] and during the administration of the salt and water retaining substances, desoxycorticosterone acetate (DCA), corticotropin (ACTH) and cortisone.

It was the purpose of the present study to determine whether marked accumulation of fluid, produced in noncardiac subjects by the administration of salt and water retaining substances, could induce cardiovascular hemodynamic alterations similar to the changes observed in naturally developing congestive heart failure. Such determinations should bear directly upon the various hypotheses of the genesis of congestive heart failure.

Methods

Cardiovascular dynamic functions were determined in the same subjects in the control state and again when maximal fluid accumulation had been produced by the administration of corticotropin or cortisone. In approximately one-half of the subjects the control determinations were made before administration of the drug, in the other half after

From the Department of Medicine, New York University College of Medicine and the Third (New York University) Medical Division, Bellevue Hospital, New York, N. Y.

Presented in part at the national meeting of the American Federation for Clinical Research, Atlantic City, N. J., May 1, 1951.

This study was supported by grants-in-aid from the National Heart Institute of the United States Public Health Service and from the Life Insurance Medical Research Fund.

completion of the diuresis and weight loss which followed discontinuation of the drug. The following hemodynamic functions were measured: cardiac output by cardiac catheterization and the direct Fick method;[11] oxygen consumption by the open method with analysis of exhaled air for oxygen and carbon dioxide by the Beckman oxygen analyzer;[12] pressures in the right heart and peripheral systemic artery by direct recording with Hamilton manometers; peripheral systemic venous pressure by saline manometer; oxygen content of arterial and right heart blood by manometric analysis;[13] "blood volume"* by the Evans Blue dye (T-1824)† dilution method[14] and electrocardiogram by string galvanometer. Body weight was determined daily. Plasma potassium and serum sodium concentrations, measured by flame photometer, were determined on the day of the hemodynamic measurements and once weekly during the period of administration of the drugs. Heart size was estimated by teleoroentgenograms of the chest taken on the day of the hemodynamic measurements.

Hemodynamic determinations were made in the morning after an overnight fast. Three successive sets of measurements were carried out with the subjects supine and at rest. The samples of exhaled air, arterial and mixed venous blood were collected over a three-minute period; the various pressures were recorded during the immediately preceding two-minute "washout" of the Tissot gasometer. The concentration of the dye T-1824 in serum was extrapolated to the time of injection from measurements on samples taken 10, 20, and 30 minutes after injection of the dye. The data presented are the averages of the three individual measurements, except in occasional instances where technical difficulties resulted in fewer determinations. Standard procedures were used in the calculations. The values for surface area were always based on the patient's edema-free weight.

Of the 14 subjects who received corticotropin, seven were convalescing from some intercurrent disease, three had rheumatoid arthritis, one had arthritis other than rheumatoid, one had lupus erythematosus disseminata and two were patients with heart disease who had just recovered from congestive heart failure with bed rest and mercurial diuretics, but without digitalis (table 1). Of the eight subjects who received cortisone, six were convalescing from an intercurrent disease, one was being treated for sarcoidosis and one for rheumatoid arthritis (table 3). Except for the two known cardiac patients, no subject had evidence of heart disease as judged from the history, physical examination, electrocardiogram or roentgenographically determined heart size. No subject was febrile during the period of study and all partook of the usual hospital ward activity. Cortisone was given orally as Cortone acetate and corticotropin as Acthar intramuscularly. The duration of administration was two to six weeks. The subjects ate the regular hospital diet without restriction or addition of salt and received 2 Gm. of potassium chloride daily.

* The shortcomings of the dye dilution technic for measurement of blood volume are keenly appreciated, but the method does give results in the same direction as more precise methods and serves, therefore, to indicate changes in blood volume.

† Generous supplies of Evans Blue dye were supplied by the Warner-Chilcott Laboratories.

Results

Almost every subject gained some weight presumably as flesh and this weight was not lost during the diuresis which followed discontinuation of corticotropin or cortisone. Since the study was focused on the effects of fluid retention, the values for fluid gain in tables 1 and 3 exclude weight gained as flesh and were derived by obtaining the difference between the maximum weight while receiving the drugs and the weight after completion of the diuresis induced by withdrawal of the drugs. Most of the subjects (10 of 14 receiving corticotropin and 3 of the 8 receiving cortisone) gained no fluid, or less than five pounds. In this category are the two undigitalized cardiac subjects who received corticotropin shortly after recovering from congestive heart failure. Five subjects, one receiving corticotropin and four cortisone, gained moderate amounts of fluid, from 9 to 14 pounds. Four subjects, three receiving corticotropin and one cortisone, gained considerable amounts of fluid, 16 to 23 pounds. Only these subjects presented clinical manifestations in any way suggesting congestive heart failure. Serum sodium and plasma potassium concentrations remained essentially unchanged in all subjects. Since the hemodynamic alterations produced by corticotropin and cortisone were largely similar, the changes produced by the two substances will be considered together.

Minimal Fluid Retention. When fluid gain was absent or small, less than 5 pounds, alterations in hemodynamic functions were likewise absent or small (tables 1, 2, 3, 4 and fig. 1). The most frequent change was a small increase in the residual pressures in the right heart, greater in right ventricular end diastolic pressure than in

TABLE 1.—*Effect of ACTH on Cardiac Output and Blood Oxygen Extraction*

Subject Sex, Age, Surface Area yrs. M.²	Diagnosis	Total* Dose	Duration Days	Fluid Gain pds.	Oxygen Consum. ml./M.²/min.	Arterial Oxygen vol. %	Mixed Venous Oxygen vol. %	A-V O_2 Diff. vol. %	Cardiac Index L./M.²/min.
.S.: M, 52, 1.70	Recovered Coryza	1.8	13	0	125	17.7	12.9	4.8	2.6
					124	17.1	12.3	4.8	2.6
.T.: M, 56, 1.85	Recovered Pneumonia	3.7	27	0	106	15.4	11.7	3.7	2.9
					137	15.3	10.9	4.4	3.1
.G.: M, 46, 1.82	Alcoholism Phlebitis	2.1	18	0	157	13.4	9.7	3.7	4.2
					149	14.4	10.6	3.8	3.9
.M.: M, 14, 1.60	Rheumatoid Arthritis	1.6	20	0	140	18.3	14.0	4.3	3.3
					134	17.8	13.5	4.3	3.1
.P.: M, 30, 1.77	No Diagnosis	4.1	21	0	110	20.3	16.1	4.2	2.6
					145	18.4	14.5	3.8	3.8
.R.: M, 50, 1.87	Bronchial Asthma	3.0	22	0	132	16.4	11.9	4.5	2.9
					122	16.6	12.4	4.2	2.9
R.S.: M, 23, 2.00	Arthritis Undiagnosed Type	2.0	16	2	172	15.8	12.0	3.8	4.5
					136	15.2	11.4	3.9	3.5
F.K.: M, 67, 1.89	Arterioscler. Heart Disease	4.1	26	3.5	124	18.6	13.1	5.5	2.3
					127	18.4	13.1	5.3	2.4
M.M.: M, 52, 1.75	Recovered Pneumonia	1.5	15	4	127	15.7	11.9	3.8	3.3
					128	14.2	10.8	3.4	3.8
A.H.: M, 61, 1.57	Arterioscler. Heart Disease	3.2	16	4	116	17.2	13.2	4.0	2.9
					167	15.5	11.7	3.8	4.4
E.R.: M, 49, 1.48	Pulmonary Fibrosis	1.8	23	9.5	160	9.7	6.0	3.7	4.3
					156	8.8	5.3	3.4	4.6
F.R.: M, 53, 1.64	Rheumatoid Arthritis	2.3	19	16	131	11.5	7.7	3.8	3.4
					127	10.3	6.8	3.5	3.6
C.R.: F, 48, 1.49	Lupus Erythematosus	3.9	39	19	150	15.9	12.1	3.8	4.0
					158	13.8	9.9	3.9	4.1
W.C.: F, 42, 1.53	Rheumatoid Arthritis	3.0	25	19	—	—	—	—	—
					—	—	—	—	—

For each subject the first set of determinations are control, the second set at peak of ACTH effect.
* Doses in thousands of units.

right atrial pressure. Femoral arterial pressure also tended to rise. Both pressure changes were more frequent in subjects receiving cortisone and largely absent in subjects receiving corticotropin. No consistent changes occurred in the other hemodynamic functions and indeed the data of these subjects served largely to indicate the satisfactory reproducibility of the measurements in the same subjects, under the conditions of the study. None of these subjects developed changes in the electrocardiogram or in heart size.

Marked Fluid Retention. The four subjects who gained more than 15 pounds of fluid all developed edema, rated as moderate in degree. Three of the subjects (F. R., W. C., T. M.) who gained 16, 19 and 23 pounds of fluid developed, in addition, slight venous congestion, mild dyspnea on exertion and orthopnea of sufficient degree to make sleep at night a little difficult. The clinical manifestations were consistent with mild congestive heart failure. In these three subjects the heart size increased appreciably and congestive changes (rales) appeared in the lungs (fig. 2). The electrocardiogram remained unchanged, except for occasional ventricular premature contractions in subject T. M. for several days at the height of the fluid gain. All of the above manifestations disappeared and the control state returned after completion of the diuresis which followed discontinuation of corticotropin or cortisone.

The marked fluid retention in these three subjects was associated with increases in vascular pressures and "blood volume" but without change in cardiac output. The in-

TABLE 2.—*Effect of ACTH on "Blood Volume" and Vascular Pressures*

Subject	Plasma Vol. L./M.²	Arterial Hct. %	"Blood Vol." L./M.²	Pressures mm. Hg					Systemic Vascular Resistance mm.Hg/L./min./M.²
				FA	PA	RV	RA	Vein	
J.S.	1.70	37.0	2.65	122/65 (82)	—	15/3	4	2	10.3
	2.09	38.0	3.36	140/71 (90)	—	25/7	5	2	11.4
G.T.	1.81	35.5	2.93	136/74 (94)	—	20/3	5	—	9.1
	1.98	37.0	3.15	141/75 (94)	21/10 (15)	21/7	5	10	8.3
L.G.	2.29	38.0	3.70	150/86 (104)	—	—	4	8	7.1
	—	—	—	148/83 (104)	—	—	2	6	7.9
C.M.	1.57	36.0	2.45	119/75 (88)	—	25/8	2	—	10.2
	—	—	—	117/75 (88)	—	—	0	10	11.0
P.P.	1.79	41.0	3.04	125/73 (90)	19/10 (12)	18/5	6	5	10.1
	1.93	40.0	3.22	150/84 (104)	20/11 (16)	22/8	6	8	8.3
J.R.	2.49	37.5	3.99	123/76 (90)	—	16/4	−3	3	9.0
	2.40	37.0	3.81	126/76 (89)	—	20/6	2	4	8.5
R.S.	—	—	—	160/90 (116)	32/10 (21)	30/4	−1	—	6.5
	1.75	39.0	2.88	160/80 (102)	28/15 (24)	27/6	5	—	7.0
F.K.	2.35	38.0	3.80	121/78 (88)	—	22/4	3	2	10.6
	2.38	35.0	3.60	152/84 (104)	—	21/2	2	2	11.9
M.M.	1.90	42.0	3.28	128/67 (88)	23/7 (15)	22/3	2	11	8.4
	2.22	38.0	3.58	141/72 (92)	21/6 (11)	24/5	2	3	7.8
A.H.	1.98	42.0	3.38	141/72 (92)	—	33/3	−2	0	12.9
	2.24	40.0	3.74	159/75 (103)	—	32/3	1	1	9.4
E.R.	2.37	31.0	3.44	113/62 (72)	56/26 (32)	57/5	−3	−4	7.8
	—	—	—	150/81 (99)	—	55/8	1	4	9.9
F.R.	2.03	30.0	2.95	125/58 (77)	—	19/3	2	11	8.0
	2.44	27.0	3.34	159/76 (96)	—	37/15	10	17	8.6
C.R.	1.85	34.0	2.80	127/74 (92)	13/3 (6)	12/1	0	0	10.5
	2.49	33.0	3.72	130/59 (82)	—	21/7	2	2	8.9
W.C.	1.72	36.0	2.69	120/70	—	—	—	5	—
	2.52	26.0	3.40	146/70	—	—	—	13	—

For each subject the first set of determinations are control, the second set at peak of ACTH effect.
Pressures in parentheses are mean pressures.
FA—femoral artery; PA—pulmonary artery; RV—right ventricle; RA—right atrium; Vein—axillary.

creases in pressure occurred in all parts of the circulatory system: (1) residual pressures in the right heart, i.e. right atrial pressure and right ventricular end diastolic pressure; (2) right ventricular systolic pressure and presumably pulmonary artery pressure; (3) systemic venous pressure and (4) systemic arterial pressure (tables 2, 4 and figs. 3 and 4). The increases in right ventricular end diastolic pressure were proportionately the most marked. "Blood volume" increased by 0.6 to 1.3 liters (tables 2 and 4). There were no changes in cardiac output or in arterial-mixed venous oxygen extraction (tables 1, 3 and figs. 3 and 4).

Subject C. R., who gained 19 pounds of fluid while receiving corticotropin, differed from the above three subjects in that she remained asymptomatic, developed smaller increases in right heart pressures and no rise in femoral artery pressure. However her "blood volume" increased by 1.3 liters. The hemodynamic changes in this patient indicate the lack of correlation between increases in vascular pressures and increases in "blood volume", a result which occurred not only in the subjects with marked fluid retention, but in all subjects studied (tables 2, 4). Increases in vascular pressures appeared more consistently related to the degree of water (and presumably salt) retention (table 5).

As expected, when the fluid gain was of

TABLE 3.—*Effect of Cortisone on Cardiac Output and Blood Oxygen Extraction*

Subject Sex, Age, Surface Area yrs. M.²	Diagnosis	Total Dose Gm.	Duration Days	Fluid Gain pds.	Oxygen Consum. ml./M.²/min.	Arterial Oxygen vol. %	Mixed Venous Oxygen vol. %	A-V O_2 Diff. vol. %	Cardiac Index L./M.²/min.
V.P.: M, 14, 1.59	Sarcoidosis	2.0	20	0	142	15.7	11.8	3.8	3.7
					143	17.2	12.6	4.6	3.1
S.N.: M, 46, 2.08	Alcoholism	4.5	29	0	—	—	—	—	—
					124	16.8	12.6	4.3	2.9
R.R.: M, 38, 1.88	Hepatic Cirrhosis	3.4	16	4	—	—	—	—	—
					150	16.7	12.6	4.1	3.7
G.A.: M, 45, 1.80	Alcoholism Neuritis	6.1	27	9	—	—	—	—	—
					128	13.6	9.2	4.4	2.9
J.Ph.: M, 38, 2.10	Recovered Pneumonia	4.2	21	10	125	16.9	13.6	3.3	3.8
					142	17.1	13.2	4.0	3.6
M.S.: M, 62, 1.89	Recovered Pneumonia	5.4	27	12	97	17.6	13.7	3.9	2.5
					120	15.5	11.2	4.3	2.8
J.Pa.: M, 53, 1.58	Recovered Pneumonia	3.8	19	14	138	15.2	10.3	4.8	2.9
					139	12.2	8.6	3.7	3.8
T.M.: M, 62, 1.71	Rheumatoid Arthritis	3.4	17	23	128	18.6	14.4	4.2	3.0
					136	15.0	10.4	4.7	2.9

For each subject the first set of determinations are control, the second set at peak of cortisone effect.

TABLE 4.—*Effect of Cortisone on "Blood Volume" and Vascular Pressures*

Subject	Plasma Vol. L./M.²	Arterial Hct. %	"Blood Vol." L./M.²	Pressures mm. Hg					Systemic Vascular Resistance mm.Hg/L./min./M.²
				FA	PA	RV	RA	Vein	
W.P.	1.58	39.5	2.61	137/92 (109)	22/10 (16)	22/3	1	—	11.6
	1.71	42.5	2.97	150/100 (117)	21/11 (15)	21/4	2	9	14.6
S.N.	—	—	—	194/110 (138)	—	—	8	—	—
	1.96	44.0	3.49	173/92 (120)	—	—	5	5	9.2
R.R.	—	—	—	—	—	—	—	—	—
	2.20	40.0	3.66	140/75 (102)	35/22 (27)	37/17	13	11	6.9
G.A.	—	—	—	—	—	—	—	—	—
	2.02	37.0	3.21	168/88 (116)	33/17 (24)	32/13	9	7	11.0
J.Ph.	2.14	39.0	3.50	140/82 (102)	21/8 (16)	21/5	3	4	6.2
	2.24	40.0	3.74	166/88 (111)	—	24/10	5	7	7.0
M.S.	1.90	43.0	3.33	137/64 (91)	—	21/4	0	—	10.3
	2.18	38.5	3.46	206/88 (123)	—	40/15	7	—	11.7
J.Pa.	1.74	40.0	2.91	122/64 (88)	24/7 (16)	20/0	−3	−4	12.8
	2.22	34.0	3.35	156/80 (109)	27/10 (18)	31/7	4	—	11.2
T.M.	1.51	40.0	2.52	145/73 (89)	—	21/6	3	5	9.7
	2.00	39.0	3.26	156/87 (104)	—	39/19	14	16	10.6

For each subject the first set of determinations are control, the second set at peak of cortisone effect.
Pressures in parentheses are mean pressures.
FA—femoral artery; PA—pulmonary artery; RV—right ventricle; RA—right atrium; Vein—axillary.

intermediate degree, 10 to 15 pounds, the hemodynamic alterations were intermediate in varying degrees between those observed in subjects with marked and minimal fluid accumulation.

Digitalis. In congestive heart failure, Digoxin administered intravenously in single therapeutic doses induces characteristically prompt falls in right heart and peripheral venous pressures and a concomitant increase in cardiac output.[15] These events have their onset approximately 15 minutes after administration of

the glycoside and their peak effect one to two hours later. When subject W. C. had gained 19 pounds of fluid as a result of corticotropin medication and was experiencing some dyspnea on exertion and orthopnea at night, she was given

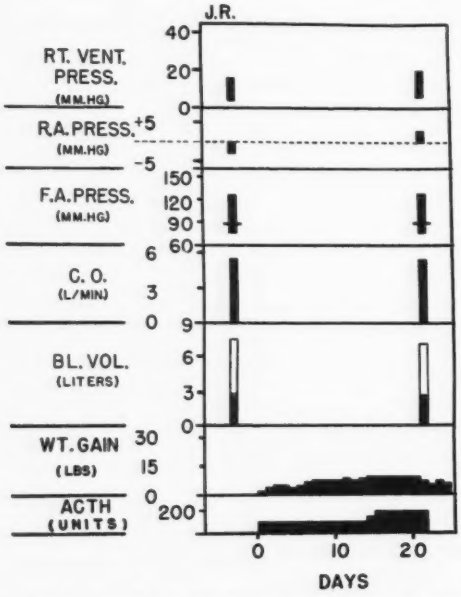


FIG. 1. Absence of significant hemodynamic alterations when corticotropin failed to induce fluid retention.

Details of plotting from top down: *right ventricular pressure*, top of column systolic pressure, bottom of column diastolic pressure; *right atrial pressure*, maximum deviation of column from zero; *femoral artery pressure*, top of column systolic pressure, bottom of column diastolic pressure, cross bar mean pressure; *cardiac output*, top of column; *blood volume*, total blood volume top of column, plasma volume open column, red cell volume solid column; *weight gain*, total gain in pounds above control weight.

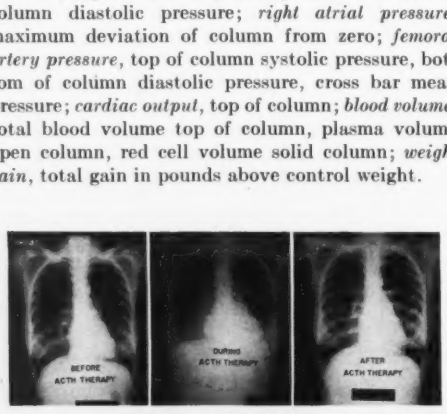


FIG. 2. Patient W. C. Note increase in heart size and development of pulmonary congestion associated with a fluid gain of 19 pounds during administration of corticotropin.

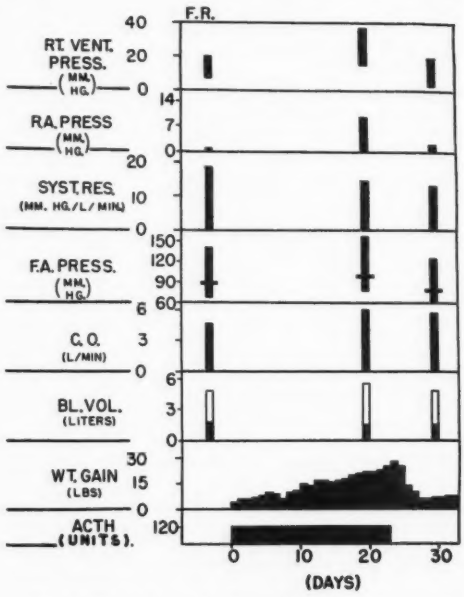


FIG. 3. Hemodynamic alterations associated with a fluid gain of 16 lb induced by administration of corticotropin. For details of plotting see legend of figure 1.

Because the hematocrit fell during administration of corticotropin, the third set of determinations was made after the diuresis which followed discontinuation of the drug. This set of determinations constitutes the preferred control for the changes induced by the corticotropin.

0.8 mg. of Digoxin intravenously without effect upon the elevated venous pressure of 170 to 180 mm. saline. Starting three hours later, 1.0 Gm. of digitalis leaf was given orally in 24 hours without reduction in the still elevated venous pressure and without initiation of diuresis or relief of symptoms, events which would have been expected in a patient with congestive heart failure. Only after corticotropin was discontinued did a diuresis with a concomitant fall in venous pressure and relief of symptoms ensue.

DISCUSSION

The observations presented suggest three points for discussion: (1) the disparity in fluid accumulation by different subjects, (2) the increase in pressure in the right heart and systemic arteries when fluid accumulation occurred and (3) the circulatory dynamics in

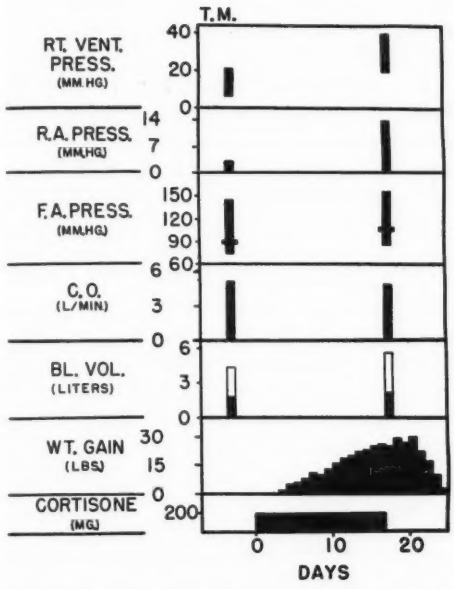


FIG. 4. Hemodynamic alterations associated with a fluid gain of 23 pounds induced by administration of cortisone. For details of plotting see legend of figure 1.

the three subjects with marked fluid accumulation and symptoms simulating mild congestive heart failure.

No explanation is apparent for the disparity in fluid gains by the different subjects. The degree of fluid retention appeared not to be related to the primary illness of the subjects, their state of convalescence, or whether corticotropin or cortisone was given. Although observations were not made in completely normal subjects, it seems unlikely that the subjects who retained large amounts of fluid had "hidden" or potential heart disease. In no subject, except the two known cardiac patients, was there evidence of heart disease. Furthermore, the failure of the two undigitalized cardiac patients, recently recovered from congestive heart failure, to retain more than minimal amounts of fluid suggests that some form of heart disease is not essential for the fluid retention. Apparently, homeostatic mechanisms promoting salt and water excretion are so potent that few subjects receiving these salt and water retaining drugs, in the doses used, retain sufficient fluid to become so edematous that congestive changes simulating congestive heart failure develop.

The most consistent hemodynamic change induced by both corticotropin and cortisone was the increase in pressure in all parts of the vascular tree. A first consideration would suggest that the pressure elevations resulted from an increase in blood volume with subsequent overdistension of the venous reservoir and right heart. However, the failure of correlation between increases in vascular pressures and changes in "blood volume" (table 5) suggests that "blood volume" is not the sole determinant of changes in pressure and that an additional factor is probably operating. A possible and attractive explanation would be that corticotropin and cortisone increased the vascular tone of the entire vascular system from arteries to veins and right heart. Such an increase in tonus could produce two effects: (1) raise the pressure in all parts of the vascular system and (2) redistribute the blood from the higher toned arterial and arteriolar side to the lesser toned, and more distensible venous side. These

TABLE 5.—*Correlation of Changes in Vascular Pressures with Changes in Fluid Gain and "Blood Volume" During Administration of ACTH and Cortisone*

The data for the two drugs have been combined

Functions Correlated*	Number of Subjects N	Correlation Coefficient r	t	p
ΔRA_m and Δ Wt.	18	0.71	2.92	0.01
ΔRA_m and Δ B.V.	14	0.26	0.92	0.38
ΔRV_d and Δ Wt.	16	0.78	2.96	0.01
ΔRV_d and Δ B.V.	14	0.45	1.62	0.14
ΔRV_s and Δ Wt.	16	0.69	2.60	0.02
ΔRV_s and Δ B.V.	14	0.41	1.47	0.2
ΔFA_m and Δ Wt.	19	0.35	1.46	0.15
ΔFA_m and Δ B.V.	14	−0.41	1.46	0.2

* The analysis is for the *changes* between control values and values at peak of drug administration for the several functions: Wt. = weight; B.V. = "blood volume"; RA_m = mean right atrial pressure; RV_d = right ventricular end diastolic pressure; RV_s = right ventricular systolic pressure; FA_m = mean femoral artery pressure.

changes could then account, in part and perhaps in full, for the observed increases in arterial, venous and residual right heart pressures.

No explanation is offered for the mechanism by which cortisone or corticotropin might increase vascular tone. The first observations were made with corticotropin and the possibility was entertained that contaminating Pitressin may have been responsible for the observed pressor effects. When cortisone produced similar increments in pressure it seemed unlikely that a contaminating known vasopressor agent was responsible for the increases in pressures. Since the rises in residual pressures in the right heart seemed to correlate better with the degree of fluid gain than with the increase in "blood volume" (table 5), the possibility should be considered that salt itself may have been the pressor agent. Neither cortisone nor corticotropin in themselves appear to possess vasopressor activity, for equally large doses, when they failed to induce fluid retention, failed also to produce rises in vascular pressures.

Since it was the purpose of this study to determine whether induced fluid retention in noncardiac subjects was associated with hemodynamic changes similar to, or different from, the hemodynamic alterations of spontaneously developing congestive heart failure, the changes in cardiovascular dynamics in the subjects with marked fluid retention deserve particular attention. In three respects the changes noted in these subjects were similar to the manifestations of naturally occurring congestive heart failure: (1) there developed the symptoms of edema, exertional dyspnea and orthopnea, (2) the "blood volume" was increased and (3) the residual pressures (atrial and ventricular end diastolic) in the right heart were elevated. The increase in right ventricular end diastolic pressure assumes particular significance since elevation of this pressure has been considered to be the criterion of congestive heart failure.[16] However, each of the above three manifestations may be considered to be nonspecific, or secondary in origin, in that they are the resultants of some other more primary physiologic change or changes. Therefore, the presence of these manifestations in two states does not necessarily indicate that both states are similarly derived.

The hemodynamic alterations associated with induced fluid retention differed markedly from the hemodynamic changes in congestive heart failure in several important, primary cardiodynamic functions. Thus, in both the corticotropin- and cortisone-induced congestion, cardiac output remained normal and arterial-mixed venous oxygen extraction, relating as it does blood supply (cardiac output) to the demand for it (oxygen consumption), also remained normal. In congestive heart failure the changes in these functions are diametrically different: cardiac output is reduced and arteriovenous oxygen difference is abnormally high. Furthermore, the failure of intravenously administered Digoxin to lower the elevated venous pressure in one patient with corticotropin-induced vascular congestion also suggests an essential difference between this type of vascular congestion and congestive heart failure, where similarly administered Digoxin promptly reduces venous and intracardiac pressures.[15] In view of these primary and more specific differences, it is difficult to consider that the vascular congestion associated with hormonally-induced fluid retention is the same entity as congestive heart failure. Both types of congested states have similar nonspecific manifestations but different specific cardiodynamic functions.

These observations suggest that the clinical manifestations and some of the hemodynamic alterations (elevation in right heart and venous pressures) traditionally considered characteristic of congestive heart failure may occur under circumstances in which cardiac output remains normal and the heart does not fail as a pump. Such noncardiac circulatory congestion simulating congestive heart failure was here produced in three subjects by inducing fluid retention with corticotropin and cortisone. The question has been raised whether the circulatory congestion present in several diseases and generally considered to be congestive heart failure may, in fact, represent other instances of noncardiac circulatory congestion simulating congestive heart failure.[17] In this category

have been placed the circulatory congestions which occur in severe, "pinch-cock", mitral stenosis,[17] acute diffuse glomerulonephritis,[5] anuria with excess fluid intake,[8] beri-beri,[18] arteriovenous fistula[18] and severe anemia.[17] In all of these instances the essential difference from congestive heart failure, as it typically occurs in a patient with heart disease, is the hemodynamic competence of the myocardium to maintain an adequate cardiac output. Such a differentiation based on primary physiologic hemodynamic functions appears warranted and seems more tenable than the traditional view which assumes that all vascular congested states are the result of myocardial insufficiency, simply because these congested states have clinical manifestations similar to congestive heart failure.

Summary

The purpose of this study was to determine whether fluid retention, induced in noncardiac subjects by means of salt and water retaining substances, produces alterations in cardiovascular dynamics similar to the changes observed in naturally occurring congestive heart failure.

In 20 noncardiac subjects, corticotropin (ACTH) was administered to 12 patients and cortisone to eight patients. Essentially similar effects were produced by the two drugs.

When fluid retention was absent or less than 5 pounds, hemodynamic changes were absent or limited to slight increases in right ventricular, right atrial and systemic arterial pressures. These pressure changes were somewhat more marked when fluid retention was more moderate, 6 to 15 pounds. In neither group did cardiac output or arteriovenous oxygen difference change.

Three subjects gained 16, 19 and 23 pounds of fluid, respectively, became edematous, developed slight cardiac enlargement and manifested in a mild form the symptoms of congestive heart failure. The associated hemodynamic changes of elevation of pressures in the right heart and systemic arteries and increases in "blood volume" were similar to the changes in these functions in congestive heart failure; however, unlike congestive heart failure, cardiac output and arteriovenous oxygen difference remained normal.

Two cardiac subjects, recently "compensated" from congestive heart failure by mercurial diuretics and rest, failed to gain fluid when given corticotropin.

In discussion, the hypothesis is explored that the circulatory congestion associated with marked fluid retention in noncardiac subjects represents not congestive heart failure, but a type of noncardiac circulatory congestion which simulates congestive heart failure. The distinction between the two states is here based on hemodynamic differences in contrast to the traditional view which assumes, on the basis of similarity of clinical manifestations, that all vascular congested states are congestive heart failure.

Acknowledgment

The authors wish to thank Mrs. Patricia Smith Burchnall, Mrs. Lydia Tucker, Miss Shirilyn Shulman and Mr. William H. Becker for their careful technical assistance, without which these observations could not have been made.

Summario in Interlingua

Le objectivo del presente studio esseva determinar si retention de fluido, inducite in individuos non-cardiac per medio de substantias retenitori de sal e aqua, produce alterationes del dynamica cardiovascular simile al alterationes observate in occurrentias natural de congestive disfallimento cardiac.

In un serie de 20 individuos non-cardiac, corticotropina (ACTH) esseva administrate a 12 patientes e cortisona a 8 patientes. Le effectos producite per le duo drogas esseva essentialmente simile.

Quando le retention de fluido esseva absente o infra 2,25 kg, le alterationes hemodynamic esseva absente o restringite a leve augmentos del pressiones dextero-ventricular, dextero-atrial, e arterio-systemic. Iste alterationes del pression esseva alique plus pronunciate quando le retention de fluido esseva inter 2,7 e 6,75 kg. Ni le un ni le altere del gruppos monstrava un alteration del ejection cardiac o del differentia atrio-ventricular de oxygeno.

Tres individuos ganiava respectivemente 7,2, 8,55, e 10,35 kg de fluido. Illes deveniva

edematose e disveloppava un leve allargamento cardiac. Illes manifestava in un forma innocue le symptomas de congestive disfallimento cardiac. In lor casos le associate alterationes hemodynamic—augmento de pression in le corde dextere e le arterias systemic e augmento del "volumine de sanguine"—esseva simile al alterationes hemodynamic in congestive disfallimento cardiac. Del altere latere, le ejection cardiac e le differentia atrio-ventricular de oxygeno remaneva normal, in contrasto con lo que se observa in congestive disfallimento cardiac.

Duo individuos cardiac, recentemente "compensate" ab congestive disfallimento cardiac per diureticos mercurial e reposo, non ganiava fluido post administrationes de corticotropina.

Nos discute le hypothese que le congestion circulatori associate con marcate retention de fluido in individuos non-cardiac representa non un forma de congestive disfallimento cardiac sed un typo de congestion circulatori non-cardiac que simula congestive disfallimento cardiac. Nostre distinction del duo statos es basate super differentias hemodynamic, in contrasto con le conception traditional que conclude super le base de simile manifestationes clinic que omne statos de congestion vascular es congestive disfallimento cardiac.

REFERENCES

[1] Warren, J. V. and Stead, E. A., Jr.: Fluid dynamics in chronic congestive heart failure. An interpretation of the mechanisms producing the edema, increased plasma volume and elevated venous pressure in certain patients with prolonged congestive failure. Arch. Int. Med. **73:** 138, 1944.

[2] Merrill, A. J.: Edema and decreased renal blood flow in patients with chronic congestive heart failure: evidence of "forward failure" as the primary cause of edema. J. Clin. Invest. **25:** 389, 1946.

[3] Starr, I.: Our changing viewpoint about congestive failure. Ann. Int. Med. **30:** 1, 1949.

[4] Gimbel, N. S., Riegel, C. and Glenn, W. W. L.: Metabolic and cardiovascular studies of prolonged intravenous administration of human serum albumin. J. Clin. Invest. **29:** 998, 1950.

[5] Davies, C. E.: Heart failure in acute nephritis. Quart. J. Med. **20:** 163, 1951.

[6] Derow, H. A.: The heart in renal disease. Circulation **10:** 114, 1954.

[7] Strauss, M. B.: Acute renal insufficiency due to lower nephron nephrosis. New England J. Med. **239:** 693, 1948.

[8] Friedberg, C. K.: Congestive heart failure of renal origin. Pathogenesis and treatment in four cases of carbon tetrachloride nephrosis. Am. J. Med. **9:** 164, 1950.

[9] Kugel, V. H.: Management of acute toxic nephrosis. Am. J. Med. **3:** 188, 1947.

[10] Albert, R. E. and Smith, W. W.: Hemodynamic effects of ACTH, DCA and cortisone compared with congestive heart failure. Am. J. Med. **12:** 111, 1952 (abstract).

[11] Cournand, A., Riley, R. L., Breed, E. S., Baldwin, E. deF. and Richards, D. W., Jr.: Measurement of cardiac output in man using the technique of catheterization of the right auricle or ventricle. J. Clin. Invest. **24:** 106, 1945.

[12] Behrmann, V. G. and Hartman, F. W.: Rapid CO_2 determination with the Beckman O_2 analyzer. Proc. Soc. Exper. Biol. & Med. **78:** 412, 1951.

[13] Van Slyke, D. D., and Neill, J. M.: The determination of gases in blood and other solutions by vacuum extraction and manometric measurement. I. J. Biol. Chem. **61:** 523, 1924.

[14] Gibson, J. G., 2nd., and Evans, W. A., Jr.: Clinical studies of the blood volume. I. Clinical application of a method employing the azo dye "Evans blue" and the spectrophotometer. J. Clin. Invest. **16:** 301, 1937.

[15] Eichna, L. W., Farber, S. J., Berger, A. R., Earle, D. P., Rader, B., Pellegrino, E., Albert, R. E., Alexander, J. D., Taube, H., and Youngwirth, S.: The interrelationships of the cardiovascular, renal and electrolyte effects of intravenous digoxin in congestive heart failure. J. Clin. Invest. **30:** 1250, 1951.

[16] Ferrer, M. I., Harvey, R. M., Cathcart, R. I., Webster, C. A., Richards, D. W., Jr. and Cournand, A.: Some effects of Digoxin upon the heart and circulation in man. Digoxin in chronic cor pulmonale. Circulation **1:** 116, 1950.

[17] Eichna, L. W., Farber, S. J., Berger, A. R., Rader, B., Smith, W. W. and Albert, R. E.: Non-cardiac circulatory congestion simulating congestive heart failure. Tr. A. Am. Physicians **67:** 72, 1954.

[18] Youmans, W. B., and Huckins, A. R.: Hemodynamics in Failure of the Circulation. American Lecture Series. Springfield, Charles C Thomas, 1950, p. 46–57.

Sodium, Potassium and Magnesium Balance During Recovery from Congestive Heart Failure due to Cor Pulmonale and Other Heart Diseases

By IVAN J. MADER, M.D., YOSHIKAZU MORITA, M.D. AND LLOYD T. ISERI, M.D.

Five cases of congestive failure due to varied causes were studied metabolically during recovery. The cases of cor pulmonale showed changes in cations and osmotically active base, similar to changes in heart failure due to other causes. A difference in the movement of water was noted between three of the present cases and the usual case of congestive heart failure.

ALTHOUGH excessive secretion of the salt-retaining corticoid, aldosterone, appears to be responsible for the ultimate retention of sodium in congestive heart failure,[1, 2, 3] the exact mechanism whereby the adrenal cortex is stimulated to secrete this steroid is not known. It is entirely conceivable that following cardiac and circulatory failure, an altered physicochemical balance of certain vital cells may initiate the train of events leading to excessive aldosterone secretion and hence to sodium retention.

Disturbances in cellular metabolism of fluid and electrolytes in congestive cardiac failure have been demonstrated previously by indirect balance methods[4, 5, 6, 7, 8, 9] and by direct tissue analysis.[10, 11, 12, 13] These studies have shown consistent cellular depletion of potassium and frequent cellular depletion of sodium. In most instances the cells also appeared to be overhydrated with water.[4, 7, 8, 11] These changes were described in high-output failure (beri-beri),[5] as well as in the usual low-output failures.

In order to determine the disturbances of cellular metabolism in various types of heart failure, a case of cor pulmonale and a case of cor pulmonale with hypertensive heart disease were studied metabolically during recovery and the results were compared with those obtained in three other cases of etiologically more common cardiac disorders. A gain in cellular potassium and sodium and inactivation of cellular base were demonstrated in these studies.

METHODS

Precise metabolic balance studies for sodium, potassium, chloride, magnesium, nitrogen and water were conducted for a total period of nine days in three cases (J. B., cor pulmonale; J. H., cor pulmonale and hypertensive heart disease; and S. L., rheumatic and hypertensive heart disease) during regression of their edema. Two other patients (A. M. and J. N.) were studied in a similar manner for all of the above components except chloride. Intake of food was limited to a special 50-mg sodium diet, previously described.[4] The exact composition of this diet was determined by direct analysis of the individual components in the final preparation. Each lot of Lonalac powder used in the preparation of the diet was analyzed.* An identical tray of food was analyzed during the last four days of study in case 5 (J. N.). Urine was collected and analyzed daily. Stools were pooled for two or three days and the studies were divided into periods of two or three days each. The amount of water drunk by the patients was measured to account for the magnesium present in tap water (0.6 mEq. per liter). Venous blood samples were obtained at the beginning of each metabolic period and at the end of the study.

From the Departments of Medicine, City of Detroit Receiving Hospital and the Wayne University College of Medicine, Detroit, Mich.

Supported in part by grants from the National Institutes of Health (H-1471), the Michigan Heart Association and the American Heart Association.

* The composition of Lonalac used in this study varied somewhat from that used in the previous study because of slight changes in the preparation of this product.

Analyses for sodium and potassium were done by flame photometry.[14] Chloride was determined titrimetrically.[15] Nitrogen was analyzed by the macro-Kjeldahl method and magnesium was determined by spectrographic[16] and colorimetric methods.[17]

Calculations were made for intracellular and extracellular partition of water and electrolytes, according to methods described by Darrow[18] and Elkinton.[19] The final extracellular volume was taken at 16 per cent of the final weight and the changes in extracellular volume were calculated backward to the beginning of each period, utilizing the plasma chloride level and chloride balance. The nonchloride space was considered to represent intracellular space, including bone tissue, but excluding collagenous connective tissue.[20] The osmolar activation of cellular base was calculated from the total balance of osmotically active bases corrected for the external balance of the bases.[7] The total osmotically active base at the end of the study was calculated as being equal to the product of the total body water, assumed to be 66 per cent of the final body weight, and the total osmotically active base concentration, determined to be equal to the sum of concentrations of plasma sodium, potassium and magnesium plus 2.5 mM. per liter for calcium. Since the nitrogen balances were near equilibrium, corrections for water, potassium and magnesium balances due to changes in protein metabolism were not made.

Cardiac, pulmonary, and renal hemodynamic studies in the patient with cor pulmonale were determined by cardiac catheterization technic.* Renal clearances of inulin and sodium paraaminohippurate were performed in the usual manner with a catheter in the right renal vein for determination of true renal plasma flow.

Case Reports

Case 1, J. B. (29106). This 51-year-old white man was admitted because of severe peripheral edema and moderate dyspnea, recurrent for two years. These manifestations were progressive and refractory to treatment for the past four weeks. There was a history of chronic cough, productive of a large amount of sputum, for 20 years prior to admission. Examination showed a patient with marked peripheral edema and moderate dyspnea. The mucous membranes were cyanotic and the neck veins were distended. The chest cage was expanded and hyperresonant to percussion. Coarse rales were audible throughout both lung fields. Examination of the heart showed right ventricular hypertrophy. The liver was moderately enlarged, but there was no ascites. X-ray films of the lungs showed marked pulmonary fibrosis and probable chronic bronchiectasis. The electrocardiogram was diagnostic of right ventricular hypertrophy. The venous pressure was 192 mm. of saline and the arm-to-tongue circulation time, using Decholin, was 26 seconds. The blood hemoglobin was 16.7 Gm. per 100 cc. and the white blood cell count was 9,000 per cubic millimeter. The urinalysis was negative and the blood urea nitrogen was 22 mg. per 100 cc. The plasma carbon dioxide content was 80 volumes per cent. The circulating plasma volume, using T-1824 dye, was 3,602 ml. and the blood volume was 6,880 ml. Cardiac and renal-vein catheterization was performed before and after evacuation of edema fluid (table 1). The findings established the diagnosis of congestive heart failure, due to chronic cor pulmonale. Metabolic studies were conducted for a period of nine days with three periods of three days each (tables 2 and 3). During the study the patient lost 7.2 Kg. of weight; there was no further loss after the study.

Table 1.—*Cardio-Pulmonary and Renal Hemodynamic Changes during Recovery from Congestive Heart Failure due to Cor Pulmonale*

	3-2-54	4-12-54
Cardiac index L./min./M.^{2}	2.72	5.10
O_2 consumption ml./min	235.	278.
Arterial O_2 content vol. %	16.3	15.4
Arterial O_2 saturation %	81.7	78.5
Pulm. capill. press. mm. Hg	13.	15.
Pulm. art. (mean) press. mm. Hg	55.	52.
Rt. vent. end. diastolic press. mm. Hg	20.	6.
Renal vein pressure mm. Hg	16.	9.
Brachial art. pressure mm. Hg	95/60	96/67
Glom. filtration rate ml./min./1.73 M.^{2}	100.7	97.3
True renal plasma flow ml./min./1.73 M.^{2}	314.0	522.5
True renal blood flow ml./min./1.73 M.^{2}	664.0	1097.0
TmPAH mg./min./1.73 M.^{2}	34.4	59.9
Extraction of PAH %	89.3	88.0

Case 2, J. H. (69228). This 67-year-old white man developed progressive shortness of breath, paroxysmal nocturnal dyspnea and peripheral edema approximately four months prior to admission. He was told that he had hypertension one year previously. Patient complained of a mildly productive cough of one year's duration. Examination revealed an undernourished patient with orthopnea, dyspnea and moderate peripheral edema. The temperature was 98 F., pulse 70 per minute, respirations 22 per minute, and blood pressure 162/90. The fundi showed changes compatible with mild hypertension. The neck veins were considerably distended. The chest was markedly emphysematous and coarse rhonchi were heard throughout. There were both right and

* Cardiac catheterization studies were made with the aid of Dr. Harper K. Hellems and his staff.

TABLE 2.—*Balance Data*

Case	Period	Days Incl.	Intake Per Period						Urine						Stool					
			H_2O L.	Na mEq	K mEq.	Mg mEq.	Cl mEq.	N Gm.	Vol. L.	Na mEq.	K mEq.	Mg mEq.	Cl mEq.	N Gm	Wt. Gm.	Na mEq.	K mEq.	Mg mEq.	Cl mEq.	N Gm.
1. J.B.	1	1–3	3.00	7.4	236.4	70.7	75.1	32.0	12.78	418.0	176.0	12.7	547.8	27.4	508	21.9	46.4	59.2	7.8	3.5
Cor	2	4–6	8.00	7.4	236.4	73.7	75.1	32.0	13.50	333.1	197.8	13.5	542.8	27.7	161	10.3	22.3	43.4	0.8	1.4
Pulm.	3	7–9	7.68	8.9	246.0	79.4	79.1	33.5	10.43	55.6	162.3	10.4	207.6	29.1	235	3.5	39.4	54.7	1.1	1.8
2. J.H.	1	1–3	2.08	7.4	236.4	70.1	75.1	32.0	5.97	291.0	149.7	21.6	383.6	26.9	232	15.5	23.3	27.6	1.9	1.7
Cor	2	4–6	2.00	7.4	236.4	70.1	75.1	32.0	5.02	174.5	179.3	17.3	283.3	21.7	1114	85.3	52.6	47.5	28.3	5.0
Pulm. Hypert.	3	7–9	2.09	7.4	236.4	70.1	75.1	32.0	2.53	46.1	133.8	17.1	134.5	21.3	914	52.9	47.5	49.4	18.4	5.5
3. S.L.	1	1–3	2.61	7.4	236.4	70.5	75.1	32.0	6.78	352.3	215.9	27.1	547.0	28.2	242	6.5	27.0	37.9	7.6	3.1
Hypert.	2	4–6	4.09	7.4	236.4	71.3	75.1	32.0	6.69	134.0	157.1	31.7	219.7	27.7	531	21.1	28.1	119.5	19.1	3.5
Rheum.	3	7–9	1.70	7.4	236.4	69.9	75.1	32.0	4.60	90.1	173.0	21.3	146.3	24.3	574	18.6	34.6	82.3	14.7	4.7
4. A.M.	1	1–3	2.40	7.4	236.4	70.1	75.1	32.0	13.81	973.3	165.9	35.6	—	30.4	507	16.8	38.8	59.2	—	3.6
Hypert.	2	4–6	2.80	7.4	236.4	70.6	75.1	32.0	8.79	511.6	214.4	22.3	—	24.1	883	40.3	50.5	64.2	—	4.5
	3	7–9	1.35	7.4	236.4	69.7	75.1	32.0	6.18	209.5	129.9	23.2	—	29.3	947	52.6	67.8	88.4	—	4.6
5. J.N.	1	1–2	1.49	5.0	157.6	46.9	—	—	3.43	331.7	65.1	10.9	—	—	978	52.2	39.2	22.4	—	—
Syph.	2	3–4	2.20	5.0	157.6	47.1	—	—	4.01	60.2	105.9	11.4	—	—	1073	52.0	52.6	29.9	—	—
	3	5–6	2.10	38.9	173.3	43.8	—	—	4.28	28.7	120.3	9.1	—	—	0	0	0	0	—	—
	4	7–8	2.10	23.2	164.7	41.1	—	—	4.01	13.6	116.5	12.6	—	—	0	0	0	0	—	—

left ventricular hypertrophy, rapid auricular fibrillation, and a harsh systolic apical murmur. The liver was enlarged 5 cm. below the right costal margin, but was not tender. Clubbing of the finger tips was present, but cyanosis was not noted. Urinalysis showed 1 plus albuminuria and occasional white blood cells in the sediment. The plasma carbon dioxide content was 55 volumes per cent, blood urea nitrogen 28 mg. per 100 cc., serum albumin 3.4 Gm., and globulin 2.5 Gm. per 100 cc. Blood hemoglobin was 16.1 Gm. per 100 cc., and the hematocrit 58.55 per cent. Circulating plasma volume was 3,353 ml., and blood volume 7,310 ml. Pneumococci (group E) were recovered from the sputum. Roentgenogram and fluoroscopic examination of the chest showed both right and left ventricular enlargement, pulmonary congestion, and chronic pulmonary emphysema. The electrocardiogram showed auricular fibrillation and left ventricular hypertrophy. The venous pressure was 195 mm. saline and the circulation time 90 seconds. It was felt that the patient had cardiac decompensation from chronic cor pulmonale and hypertensive heart disease. The patient was digitalized and started on metabolic studies, using a synthetic 50 mg. sodium diet. There was a 3.5 Kg. weight loss and moderate improvement of dyspnea and edema. After completion of the studies, there was an additional weight loss of 8.0 Kg.

Case 3, S. L. (12116). This 36-year-old white woman was admitted with severe congestive heart failure for the third time in one year. Shortness of breath, followed by peripheral edema, was first noted three years earlier, at which time she was discovered to have hypertension and rheumatic heart disease. The examination revealed an orthopneic dyspneic patient with moderately severe peripheral edema. The heart was enlarged both to the right and left and revealed the characteristic murmurs of mitral insufficiency and stenosis. There was also a murmur of tricuspid insufficiency with a pulsatile liver. Rales were audible at both lung bases. The blood pressure was 234/140. The venous pressure was 256 mm. saline and the arm-to-tongue circulation time 53 seconds. The patient was placed on the synthetic low sodium (50 mg.) diet for nine days and Mercuhydrin was given on the second, fifth and eighth days. The patient lost 3.8 Kg. during the study and 4.9 Kg. more after the study.

Case 4, A. M. (68415). A 59-year-old white man was admitted because of peripheral edema and dyspnea on exertion, gradually progressive for the previous two months. Examination showed temperature 98.6 F., pulse 92 per minute, respirations 24 per minute, and blood pressure 148/118. The fundi showed grade II hypertensive changes. The discs showed secondary optic atrophy. Neck veins were distended. Marked enlargement of the heart was noted and a harsh grade II systolic murmur was heard over the mitral area. Bilateral basal rales were present and the liver was enlarged 5 cm. below the costal margin. The extremities showed marked

TABLE 3.—*Derived Data*

Case	Period	Days Inc.	Body Wt. Kg.	Water Bal. Kg.			Sodium Bal. mEq.			Potassium Bal. mEq.			Magnesium Bal. mEq.			Δ Osm. Active Base	Plasma Electrolytes mEq./L.			
				Total	Extracell.	Intracell.	Total	Extracell.	Intracell.	Total	Extracell.	Intracell.	Total	Extracell.	Intracell.		Na	K	Mg	Cl
1.	1	1–3	64.5	−5.0	−5.9	+0.9	−432.4	−820.9	+388.5	+14.0	−21.5	+35.5	−1.2	−9.6	+8.4	−246.7	144.2	4.55	1.22	95.1
J.B.	2	4–6	59.5	−2.2	−3.1	+0.9	−336.0	−501.3	+165.3	+16.3	−11.8	+28.1	+16.8	−0.1	+16.9	−167.1	146.3	4.93	1.05	102.0
	3	7–9	57.3	0	−1.9	+1.9	−50.2	−346.2	+296.0	+44.3	−12.5	+56.8	+14.3	−1.4	+15.7	−324.3	142.0	5.24	1.33	87.1
(Final or total)			57.3	−7.2	−10.9	+3.7	−818.6	−1668.4	+849.8	+74.6	−45.8	+120.4	+25.9	−11.1	+41.0	−738.1	133.7	4.97	1.46	92.0
2.	1	1–3	66.5	−0.8	−2.3	+1.5	−299.1	−385.9	+86.8	+63.4	−10.2	+73.6	+20.9	−2.1	+23.0	−87.8	144.9	5.17	1.38	107.9
J.H.	2	4–6	65.7	−2.4	−2.1	−0.3	−252.4	−317.3	+64.9	+4.5	−16.7	+21.2	+5.3	−2.4	+7.7	−150.1	141.5	5.28	1.45	103.7
	3	7–9	63.3	−0.3	−0.8	+0.5	−91.6	−112.0	+20.4	+55.1	+10.6	+44.5	+3.6	−2.5	+5.5	+36.0	140.0	4.86	1.50	102.5
(Final or total)			63.0	−3.5	−5.2	+1.7	−643.1	−815.2	+172.1	+123.0	−16.3	+139.3	+29.8	−7.0	+36.2	−201.9	140.0	6.01	1.40	102.5
3.	1	1–3	67.7	−1.9	−3.2	+1.3	−351.4	−493.5	+142.1	−6.5	−22.0	+15.5	+5.5	−4.4	+9.9	−45.0	144.9	4.54	1.27	113.0
S.L.	2	4–6	65.8	−1.6	−1.3	−0.3	−147.7	−232.2	+84.5	+51.2	−5.7	+56.9	−79.9	−4.8	−75.1	−230.8	142.9	4.04	1.25	104.6
	3	7–9	64.2	−0.3	−0.8	+0.5	−101.3	−88.6	−12.7	+28.8	−0.4	+29.2	−33.7	+2.9	−36.6	+129.7	140.0	4.02	1.02	103.0
(Final or total)			63.9	−3.8	−5.3	+1.5	−600.4	−814.3	+213.9	+73.5	−28.1	+101.6	−108.1	−6.3	−101.8	−146.1	141.5	4.31	1.31	102.5
4.	1	1–3	68.3	−10.1	—	—	−982.7	—	—	+31.7	—	—	−24.7	—	—	−541.4	142.3	4.27	1.48	—
A.M.	2	4–6	58.2	−4.4	—	—	−544.5	—	—	−28.5	—	—	−15.9	—	—	−152.0	142.0	4.72	1.57	—
	3	7–9	53.8	−2.5	—	—	−254.7	—	—	+38.7	—	—	−41.9	—	—	−143.8	140.0	4.65	1.55	—
(Final or total)			51.4	−16.9	—	—	−1781.9	—	—	+41.9	—	—	−82.5	—	—	−836.6	140.0	4.41	1.55	—
5.	1	1–2	63.5	−2.1	—	—	−378.9	—	—	+53.3	—	—	+13.6	—	—	—	150.0	4.27	—	—
J.N.	2	3–4	61.4	−1.4	—	—	−107.2	—	—	−0.9	—	—	+5.8	—	—	—	—	—	—	—
	3	5–6	60.0	+1.0	—	—	+10.2	—	—	+53.0	—	—	+34.7	—	—	—	—	—	—	—
	4	7–8	61.0	−0.1	—	—	+9.6	—	—	+48.2	—	—	+28.5	—	—	—	—	—	—	—
(Final or total)			60.9	−2.6	—	—	−466.9	—	—	+153.6	—	—	+82.6	—	—	−67.5	150.0	5.82	1.55	—

edema. The venous pressure was 207 mm. saline and the circulation time 64 seconds. Circulating plasma volume was 4,471 ml. and blood volume 8,003 ml. The blood urea nitrogen was 32 mg. per 100 cc., serum albumin 3.1 and globulin 2.4 Gm. per 100 cc., plasma carbon dioxide content 53 vol. per cent, and fasting blood sugar 72 mg. per 100 cc. The blood hemoglobin was 13.3 Gm. per 100 cc. The electrocardiogram showed left ventricular hypertrophy. A diagnosis of hypertensive heart disease with congestive heart failure was made and the patient was studied for nine days, during which time there was a weight loss of 16.9 Kg. No further loss occurred after the study. The venous pressure at the end of the study was 61 mm. saline and the circulation time 25 seconds.

Case 5, J. N. (24063). This 62-year-old white man was admitted because of paroxysmal nocturnal dyspnea and peripheral edema. These symptoms were first noted one year previously, but did not recur until one week before admission. The patient had also noted intermittent claudication for the past year. Examination showed an orthopneic edematous patient with a blood pressure of 190/95, temperature 98 F., pulse 85 per minute and respirations 20 per minute. Fine rales were present in both lungs. The heart was enlarged to the anterior axillary line and a to-and-fro murmur was heard in the aortic area. Pulsations of the dorsalis pedis artery were weak. The roentgenogram of the heart showed an enlarged left ventricle and an aneurysmal dilatation of the ascending aorta with calcific deposition in this segment. The blood serology was positive for syphilis, blood urea nitrogen 19 mg. per 100 cc., and serum albumin 3.8 and globulin 1.8 Gm. per 100 cc. Diagnoses of hypertensive and syphilitic heart disease with congestive heart failure and atherosclerosis obliterans were made and the patient was studied metabolically for eight days for sodium, potassium and magnesium balances. There was a total weight loss of 2.6 Kg. during the study.

Results of the Metabolic Studies

The results of the metabolic studies carried out during recovery from congestive failure in the proven case of cor pulmonale and in the other four cases are presented in table 2. The derived values for intracellular and extracellular changes in the first three cases are presented in table 3.

Changes in Sodium Metaoblism

As would be expected, sodium was eliminated in considerable quantities. The total external balance in the case of cor pulmonale (case 1) amounted to −818.6 mEq. during the nine-day period of study, with most of the sodium being eliminated during the first six days. A total of −643.1, −600.4, −1,781.9 and −466.9 mEq.

of sodium was lost externally by cases 2, 3, 4 and 5, respectively. Calculations possible only in the first three cases showed that the amount of sodium lost externally was less than the calculated loss of sodium from the extracellular compartment. A significant quantity of sodium thus entered a nonchloride space (presumably the cell) during the period of recovery, 849.8 mEq. in case 1, 172.1 mEq. in case 2, and 213.9 mEq. in case 3.

Changes in Potassium and Magnesium Metabolism

A slight, but distinctly positive, balance of potassium, +74.6, +123.0, +73.5, +41.9, and +153.6 mEq., was observed in cases 1 to 5, respectively. Since there was some loss of potassium from the shrinking extracellular space, the total positive intracellular balance in those cases in which calculation was possible was slightly greater than the observed external balance. Case 1, with cor pulmonale, showed a positive intracellular potassium balance of +120.4 mEq.; case 2, +139.3 mEq. and case 3, +101.6 mEq.

A positive balance of magnesium was observed in cases 1, 2 and 5, but a negative balance was seen in cases 3 and 4.

Changes in Water Metabolism

Total loss of water, as judged by loss of weight during the eight- to nine-day period, varied from 2.6 to 7.2 Kg. Calculations in the first three cases indicated a loss of extracellular water amounting to −10.9, −5.2 and −5.3 L., and a slight gain of intracellular water of +3.7, +1.7 and +1.5 L. in cases 1, 2 and 3, respectively.

Osmotic Activation of Intracellular Base

The net change of total osmotically active base, corrected for external balances of sodium, potassium and magnesium, will determine the net changes in osmotically active intracellular base, since electrolytes in the extracellular fluid are, for practical purposes, osmotically completely active. A net change with a negative value will imply inactivation of the cellular base and a positive value will indicate activation of the cellular base elements.

In all five cases a distinctly negative value of osmotic activity was obtained, −738.1, −201.9 −146.1, −836.6 and −67.5 mM, respectively.

Discussion

The diagnosis of chronic cor pulmonale in congestive heart failure in case 1 was made clinically from the history and physical signs, and was established by cardiac catheterization, with the findings of a normal pulmonary "capillary" pressure, an elevated pulmonary artery, right ventricular end-diastolic, right auricular and renal vein pressures, a relatively normal cardiac index, and an oxygen-desaturated arterial blood. Following diuresis and weight loss of 7.2 Kg., evidence of right ventricular failure disappeared, but the pulmonary artery pressure remained elevated. The cardiac index rose to a supernormal level, compatible with the diagnosis of chronic pulmonary disease with cor pulmonale. The total oxygen consumption of 235.2 ml. per minute, the absence of a purulent sputum, and the absence of fever or leukocytosis ruled out the possibility of a superimposed acute infection complicating the picture of cor pulmonale. It is interesting to note that renal hemodynamic studies showed a glomerular filtration rate within the normal range at the height of congestive heart failure and an almost identical filtration rate after recovery from failure. Observations, such as this, indicate that tubular activity is more important in the pathogenesis of sodium and water retention than changes in glomerular filtration rate.

Metabolic studies carried out on this patient revealed, in addition to extracellular evacuation of sodium and water, a cellular uptake of all three electrolytes, sodium, potassium and magnesium (1,007 mEq. or 988.5 mM total), far in excess proportionately to the gain in cellular water (3.7 L.). The fluid entering the cells was thus hypertonic and composed of cations in a concentration of 262 mM. per liter, with the sodium ion comprising the major share (230 mM. per liter). Comparison of cases 2 and 3 with case 1 revealed a qualitative similarity in regard to the fluid entering the cell during recovery, but the concentration of

cations was not as high (195 mM. per liter in case 2 and 174 mM. per liter in case 3) and the concentration of sodium was decidedly lower (101 mM. per liter in case 2 and 142 mM. per liter in case 3). The greater propensity for gain in cellular sodium found in case 1 could have been due partly to the nature of the underlying disease responsible for congestive failure, since it has been shown recently that acidosis of respiratory origin is buffered to a significant degree by the emergence of base from the intracellular compartments.[21, 22] If such a mechanism had been operating in case 1 during development of congestive failure, it would be relatively simple to explain the greater uptake of sodium by the cells, coincident to improvement in the cardiopulmonary function.

Apparently emergence of magnesium from the cells during recovery from congestive failure was not responsible for migration of sodium and potassium into the cells, since in three of the patients a positive magnesium balance was observed. In two patients a negative balance was found. In case 3, the negative balance was caused primarily by loss of magnesium in the stools, as well as by periodic loss of magnesium in the urine, following Mercuhydrin injections. Whether or not Mercuhydrin contributed toward excess fecal loss could not be determined from the data on hand. The external loss of magnesium in this patient was accompanied by a fall in the serum magnesium to subnormal levels, a phenomenon frequently observed during rapid mercurial diuresis.[23, 24] A negative balance of magnesium observed in case 4 was apparently not due to Mercuhydrin, since the patient had received no diuretic agents. Urinary loss of magnesium, however, was quite considerable. In this particular case, the negative balance of magnesium could have reflected the elimination of magnesium retained by renal decompensation prior to the onset of study. The volume of urine or the total weight of the stools appeared to have no definite influence on the loss or gain of magnesium during recovery from cardiac failure. If these two cases (cases 3 and 4) with a negative magnesium balance are regarded as exceptions to the rule because of interfering factors, it can be concluded that a positive magnesium balance occurs during recovery from congestive heart failure.

Movements of water and cations in all three cases were such that the intracellular osmolarity tended to increase during recovery from congestive failure. Since osmotic equilibrium between the cells and the extracellular fluid can be assumed to be maintained at all times, any tendency toward a rise in intracellular osmolarity would necessitate either a rise in osmolarity of the intracellular fluid, migration of water into the cells, or an osmotic inactivation of the free base residing within or entering the cells. Since the osmolarity of the extracellular fluid tends to fall during recovery from congestive failure,[25] the first two possibilities appear unlikely. Measurements made according to the method of Elkinton[7] consistently showed inactivation of intracellular base in all five cases during recovery from failure. The relative magnitude of this change with respect to total weight loss was the greatest in case 1, suggesting again the possibility of some effect conditioned by decompensated respiratory acidosis.

The question of whether migration of sodium and potassium into the cells (possibly in exchange for hydrogen ions) had caused inactivation of cellular base, or whether the inactivation of cellular base had occurred first and had caused transfer of sodium and potassium into the cells, remains problematic. There is no reason to doubt that both events could have occurred simultaneously in a given patient recovering from congestive heart failure. Transfer of water in the first situation would be into the cells and in the second situation, out of the cells. With both events taking place simultaneously, the direction of transfer of water would depend upon the more prominent factor. Of the three cases in which calculations of water transfer were possible, patient J. B. (case 1), showing 3.7 L. net gain of cellular water, had severe respiratory acidosis, as well as congestive failure. Correction of the acidosis may have resulted in migration of additional sodium and potassium back into the cells, causing iso-

osmotic transfer of water in the same direction. The magnitude of this transfer during recovery may have been so great as to overcome the tendency for water to leave the cell, due to primary inactivation of the intracellular base. The small net transfer of water into the cells in case 2, with hypertension and cor pulmonale, may also have been influenced by a low grade respiratory acidosis, which could not be demonstrated in the plasma carbon dioxide content. In case 3, mercurials were used frequently, so that shifts of water during recovery do not necessarily represent correction of an altered intracellular balance. A positive balance of intracellular water was also seen during recovery in one of the three beriberi cases studied previously.[5] Minor changes in intracellular water were likewise seen in three of the seven cases previously studied, who had less than 3 Kg. of total fluid loss.[4] In general, only patients with marked fluid loss (greater than 8 Kg.) during recovery from uncomplicated congestive heart failure show a significant loss of intracellular water.[4] It is very probable that certain factors other than that associated with recovery from congestive heart failure per se may account for the uptake of water by the cells.

It would seem from these studies that the metabolic changes in congestive heart failure due to chronic cor pulmonale are essentially the same as in failure due to other causes. The cells appear to be deficient rather than overladen with water and depleted of more sodium, presumably due to complicating respiratory acidosis.

The exact mechanism for retention of sodium and water progressing to cardiac edema remains obscure, but the intrinsic osmotic activation of cellular base following cardiac and circulatory failure may in some way set in motion the train of events leading to this clinical condition. It is postulated[26] that the increase in osmolarity of the cells and, temporarily, the relative decrease in osmolarity of the extracellular fluid provoke aldosterone activity to sodium retention, whereas the increase in osmolarity of the cells or the obligatory increase in osmolarity of the extracellular fluid[26] provoke antidiuretic activity and water retention.

Summary

Five cases of congestive heart failure were studied metabolically during recovery. One unequivocal case and one probable case of cor pulmonale showed cellular uptake of sodium, potassium and magnesium and inactivation of cellular base in a manner similar to heart failure due to other causes. Cellular uptake of water during recovery, calculable in three cases, was contrary to previous findings, but was explainable by the greater than usual uptake of cations by the cells associated with chronic pulmonary insufficiency or by the frequent use of mercurial injections. The pathogenesis of congestive cardiac edema is discussed.

Acknowledgment

We are grateful to Drs. Clayton Shors and David Young and to Mrs. Maxine Adams, Mrs. Nancy Davenport and Mrs. Juanita Maxwell for their valuable assistance in conducting this study.

Summario in Interlingua

Cinque casos de congestive disfallimento cardiac esseva studiate metabolicamente durante le periodo del recuperation. Un caso inequivoc e un altere probabile de corde pulmonal monstrava un reception cellular de natrium, kalium, e magnesium e un inactivation del base cellular que esseva simile a correspondente phenomenos in casos disfallimento cardiac debite a altere causas. Le reception cellular de aqua durante le periodo de recuperation esseva calculate in tres casos e non se trovava de accordo con previe constatationes. Iste discrepantia esseva explicabile per le reception supra-usual de cationes in le cellulas que es associate con chronic insufficientia pulmonar o per le frequente uso de injectiones mercurial. Es discutite le pathogenese de congestive edema cardiac.

REFERENCES

[1] Luetscher, J. A., Jr. and Johnson, B. B.: Observations on the sodium-retaining corticoid (aldosterone) in the urine of children and adults in relation to sodium balance and edema. J. Clin. Invest. **33:** 1441, 1954.

[2] Singer, B. and Wener, J.: Excretion of sodium-

retaining substance in patients with congestive heart failure. Am. Heart J. **45:** 795, 1953.

[3] DEMING, G. B. AND LUETSCHER, J. A., JR.: Bioassay of Desoxycorticosterone-like material in urine. Proc. Soc. Exper. Biol. & Med. **73:** 171, 1950.

[4] ISERI, L. T., BOYLE, A. J. AND MYERS, G. B.: Water and electrolyte balance during recovery from severe congestive failure on a 50 milligram sodium diet. Am. Heart J. **40:** 706, 1950.

[5] —, UHL, H. S. M., CHANDLER, D. E., BOYLE, A. J. AND MYERS, G. B.: Fluid and electrolyte balance during recovery from high-output heart failure due to beri-beri. Circulation **9:** 247, 1954.

[6] SINCLAIR-SMITH, B., KATTUS, A. A., GENEST, J. AND NEWMAN, E. V.: The renal mechanism of electrolyte excretion and the metabolic balances of electrolytes and nitrogen in congestive heart failure: The effects of exercise, rest and amino phylline. Bull. Johns Hopkins Hosp. **84;** 369, 1949.

[7] SQUIRES, R. D., CROSLEY, A. P., JR. AND ELKINTON, J. R.: The distribution of body fluids in congestive heart failure. III. Exchanges in patients during diuresis. Circulation **4:** 868, 1951.

[8] MILLER, G. E.: Water and electrolyte metabolism in congestive heart failure. Circulation **4:** 270, 1951.

[9] SCHROEDER, H. A.: Studies on congestive circulatory failure. III. The relations of edema to urinary chlorides. Circulation **1:** 481, 1950.

[10] ISERI, L. T., ALEXANDER, L. C., MCCAUGHEY, R. S., BOYLE, A. J. AND MYERS, G. B.: Water and electrolyte content of cardiac and skeletal muscle in heart failure and myocardial infarction. Am. Heart J. **43:** 215, 1952.

[11] TALSO, P. J., SPAFFORD, N. AND BLOW, M.: The metabolism of water and electrolytes in congestive heart failure. II. The distribution of water and electrolytes in skeletal muscle in edematous patients with congestive heart failure before and after treatment. J. Lab. & Clin. Med. **41:** 405, 1953.

[12] MOKOTOFF, R., ROSS, G. AND LEITER, L.: The electrolyte content of skeletal muscle in congestive heart failure. A comparison of results with inulin and chloride as reference standards for extracellular water. J. Clin. Invest. **31:** 291, 1952.

[13] ISERI, L. T., BOYLE, A. J., CHANDLER, D. E. AND MYERS, G. B.: Electrolyte studies in heart failure. I. Cellular factors in the pathogenesis of the edema of congestive heart failure. Circulation **9:** 615, 1955.

[14] MOSHER, R. E., BOYLE, A. J., BIRD, E. J., JACOBSON, S. D., BATCHELOR, T. M., ISERI, L. T. AND MYERS, G. B.: The use of flame photometry for the quantitative determination of sodium and potassium in plasma and urine. Am. J. Clin. Path. **19:** 461, 1949.

[15] SCHALES, O. AND SCHALES, S. S.: A simple and accurate method for the determination of chloride in biological fluids. J. Biol. Chem. **140:** 879, 1941.

[16] BOYLE, A. J., WHITEHEAD, T., BIRD, E. J., BATCHELOR, T. M., ISERI, L. T., JACOBSON, S. D. AND MYERS, G. B.: The use of the emission spectrograph for the quantitative determination of Na, K, Ca, Mg and Fe in plasma and urine. J. Lab. & Clin. Med. **34:** 625, 1949.

[17] FISTER, H. J.: Manual of Standardized Procedures for Spectrophotometric Chemistry. New York, Standard Scientific Supply Corp., 1950.

[18] DARROW, D. C.: Retention of electrolytes during recovery from severe dehydration due to diarrhea. J. Pediat. **28:** 515, 1946.

[19] ELKINTON, J. R., WINKLER, A. W. AND DANOWSKI, T. S.: Transfers of cell sodium and potassium in experimental and clinical conditions. J. Clin. Invest. **27:** 74, 1948.

[20] NICHOLS, G., JR., NICHOLS, NANCY, WEIL, W. B. AND WALLACE, W. M.: The direct measurement of the extracellular phase of tissues. J. Clin. Invest. **32:** 1299, 1953.

[21] GIEBISCH, G., BERGER, L. AND PITTS, R. F.: The extrarenal response to acute acid-base disturbances of respiratory origin. J. Clin. Invest. **34:** 231, 1955.

[22] COOKE, R. E., COUGHLIN, F. R., JR. AND SEGAR, W. E.: Muscle composition in respiratory acidosis. J. Clin. Invest. **31:** 1006, 1952.

[23] MARTIN, H. E., MEHL, J. AND WERTMAN, M.: Clinical studies of magnesium metabolism. M. Clin. North America **36:** 1157, 1952.

[24] ISERI, L. T.: Personal observations.

[25] —, MCCAUGHEY, R. S., ALEXANDER, L., BOYLE, A. J. AND MYERS, G. B.: Plasma sodium and potassium concentrations in congestive heart failure. Relationship to pathogenesis of failure. Am. J. M. Sc. **224:** 135, 1952.

[26] —, MADER, I. J. AND BOYLE, A. J.: Electrolyte studies in heart failure. II. Extracellular factors in the pathogenesis of congestive edema. Circulation **9:** 620, 1955.

Report of Committee on Nomenclature of The American Society for the Study of Arteriosclerosis

Tentative Classification of Arteriopathies

IT is recognized that all classifications of diseases are tentative and subject to change as new contributions alter concepts of etiology and pathogenesis. This classification is presented as a summary of current opinions not only of the members of the committee but of many other physicians who have been interested in and have worked with various phases of the broad problem of arterial diseases.

This proposed classification covers a restricted area and aims at a concise definition of clinical pathological entities rather than an all-inclusive coverage of the whole area of vascular lesions, the functional as well as the organic.

There is no frank conflict between this classification of arteriopathies and the one distributed by the American Heart Association. It neither does nor does not have the endorsement of the A. H. A.

A. Degenerative Arteriopathies

1. Atherosclerosis

A disease, primarily of large arteries, characterized by plaquelike intimal deposits which contain neutral fat, cholesterol, lipophages, and sometimes blood or other evidence of hemorrage. The lesions may remain stationary or enlarge, fibrose or calcify. They may encroach upon the lumen. The intimal surface commonly degenerates, predisposing to thrombotic occlusion. Factors which are considered in the pathogenesis are:

(1) Heredity, sex, body type and age,
(2) Disturbance in lipid and carbohydrate metabolism,
(3) High caloric and high fat intake,
(4) Various endocrinopathies,
(5) Intravascular pressure and
(6) Mural lesions.

2. Medial Calcific Sclerosis (Moenckeberg's)

A disease characterized by widespread focal calcification and fibrosis in the media of muscular arteries particularly in the legs. The calcification sometimes appears as circumferential rings. This is most commonly a disease of adult life which tends to progress with aging. The etiology is unknown. Reduction of the arterial lumen is rare but may occur usually from concomitant atherosclerosis.

3. Arterionecrosis

(1) *Cystic Medionecrosis.* A disease characterized by myxomatous degeneration, often with cyst formation, of the medial coat of the aorta. It is the major cause of dissecting aneurysms and thus sometimes of aortic insufficiency. The etiology is unknown. The condition may occur in adults of any age; it has an increased incidence in the terminal months of pregnancy and is associated with hypertension.

(2) *Toxic Arterionecrosis.* A state characterized by degenerative and necrotic lesions in various parts of all of the coats of the arteries ascribed to exogenous or, possibly, endogenous (renal, adrenal) toxins.

(3) *Arterionecrosis of Physical Origin.* Arterionecrosis produced by gross mechanical or thermal trauma.

(4) *Arteriolar Necrosis (Arteriolonecrosis).* The characteristic lesion of hypertensive disease of varied origins which is clinically manifest as 'malignant' or 'accelerated' hyperten-

sion. The most severe changes are found in renal intralobular arteries and afferent arterioles, although lesions occur in other regions (splanchnic and renal arterioles). The essential lesion is intramural fibrinoid necrosis, often associated with perivascular fibrinoid smudges and with corresponding zones of hemorrhage and intravascular thrombosis. These changes are usually superimposed on hyperplastic arteriopathy. Arterial hypertension is a basic common factor in the genesis of arteriolar necrosis, although endogenous toxic factors seem to predispose to its occurrence, sometimes in the absence of severe increases of arterial pressure.

B. Productive or Hyperplastic Arteriopathy (Hypertensive Vascular Disease

Abnormalities primarily affecting systemic small arteries and arterioles. In arteries, these are manifested by muscular hyperplasia which progresses to medial fibrosis, reduplication of the internal elastic lamina and intimal proliferation; in arterioles, there appear muscular hyperplasia and, later, hyaline degeneration. These are associated with, or result from, increased arterial pressure. Pulmonary arteries may be involved in diseases associated with increased pulmonary arterial pressure. In such conditions, remediable thickening of vessel walls may be observed.

C. Inflammatory Arteriopathies

1. Infectious

(1) *Syphilitic.* Widespread vascular abnormalities characterized primarily by adventitial cellular infiltration, especially by plasma cells. The principal defects are manifest in the thoracic aorta and meningeal vessels. In the aorta, the gross changes follow on obliteration of vasa vasorum and consist in destruction of the elastica with a tendency to aneurysm formation or valvular insufficiency of the aortic commissures.

(2) *Bacterial.* Local acute inflammatory and destructive changes in arteries throughout the body. These follow on local invasion of various bacteria, particularly pathogenic cocci. Mycotic aneurysm often develop at the sites of damage.

(3) *Plasmodial.* This usually involves small arteries and is associated with agglutination of red cells in cases of severe or terminal malarial infestation.

(4) *Viral.* Arteritis, usually involving small arteries, and caused by local damage by rickettsial and virus infections.

2. Attributable to Abnormal Tissue Responses (Hypersensitivity)

(1) *Polyarteritis Nodosa (periarteritis nodosa;* essential panarteritis). Characterized by inflammation of small arteries with cellular infiltration, at first mainly periarterial, with subsequent segmental necrosis of the medial coat. Aneurysms may develop in the weakened vessels; healing is by fibrosis or obliteration. Many cases represent hypersensitivity reactions to drugs, antibiotics, foreign protein or unknown agents.

(2) *Arteritis Associated with Systemic Lupus Erythematosus.* Part of a widespread disease characterized by collagen necrosis, low grade inflammatory changes, and, sometimes, intimal proliferation and thrombosis.

(3) *Arteritis Associated with Scleroderma and Acrosclerosis.* Affecting small and medium sized arteries, usually of the extremities, and characterized by fibrosis of the adventitia, slow endothelial proliferation and arterial occlusion which may lead to tissue ischemia and sometimes gangrene.

(4) *Arteritis Associated with Rheumatic Fever.* Inflammatory and productive arteritis complicating rheumatic fever and manifesting itself mainly in coronary, cerebral or renal arteries.

(5) *Thromboangiitis Obliterans.* A recurrent segmental, obliterative panangiitis involving the arteries and veins of extremities, rarely of the viscera. It occurs almost exclusively in young adult males and leads to tissue ischemia and sometimes gangrene. The complete etiology is unknown; currently the use of tobacco by sensitive individuals is considered the most important etiologic factor.

(6) *Cranial Arteritis.* (Giant-cell arteritis; temporal arteritis) A panarteritis present chiefly in the arteries of the head and scalp and occasionally in those of other parts of the body.

The lesions have the histologic appearance of granulomas, contain giant cells and produce considerable periarterial inflammation and sometimes endothelial proliferation. This may go on to vascular occlusion which may be precipitated by earlier thrombosis. It is seen almost exclusively in the elderly in whom it causes headache and sometimes sudden loss of vision, more rarely loss of hearing. The etiology is unknown.

3. Traumatic Arteritis

(1) *Chemical.* Arteritis associated with or resulting from chemical injuries of the arteries, and due either to local contact from injection of chemical solutions or indirectly to the absorption of toxic chemicals.

(2) *Physical.* Arteritis resulting from exposure to various physical agents: light, heat, cold, x-ray and radioactive substances.

(2) *Mechanical.* Arteritis due to mechanical injury by direct impact or as a result of cavitation from high-velocity missile wound.

4. Undetermined or Uncertain Origin

(1) *Thrombotic Thrombocytopenic Purpura.* A relatively uncommon disease of the arterioles and capillaries characterized pathologically by collagen changes in the intima which are associated with localized endothelial proliferation, extensive platelet deposition and occlusion of involved vessels. There is secondary thrombocytopenia with purpura.

(2) *Nodular Vasculitis.* Occurs chiefly in older women and belongs to the category of nontuberculous nodosities. The lesions are more painful, of shorter duration and have less tendency to ulcerate than those seen in erythema induratum. The histologic picture, however, is similar to erythema induratum.

(3) *Aortic Arch Arteritis* (Young female arteritis; pulseless disease). A relatively rare proliferative arteritis involving the intimal and medial coats, affecting almost exclusively the aortic arch and its major branches, often leading to thrombosis and occlusion of one or more of these branches; sometimes occlusion of the coronary ostia develops. The condition occurs almost exclusively in young or middle aged women. The etiology is unknown.

D. Primary Thromboembolic Arteriopathies

1. Embolism

(1) Detached thrombus or vegetation
(2) Air
(3) Fat
(4) Foreign bodies

2. Essential Arteriothrombosis (in situ)

Such as is seen in *polycythemia vera* and other conditions where there is hypercoagulability of the blood.

E. Combined Forms of Arteriopathies

Combination of any of the aforementioned arteriopathies. The combination of atherosclerosis and medial arteriosclerosis or arterionecrosis is frequent, and suggest that medial lesions may often determine the localization of atheroma in susceptible individuals.

The Committee on Nomenclature of The American Society for the Study of Arteriosclerosis.
Joseph B. Wolffe, M.D. (Chairman)
Nelson W. Barker, M.D.
Arthur C. Corcoran, M.D.
G. Lyman Duff, M.D.
Howard B. Sprague, M.D.

CLINICAL PROGRESS

EDITOR: HERRMAN L. BLUMGART, M.D.

Associate Editor: A. STONE FREEDBERG, M.D.

Aortic Dissection (Dissecting Hematoma; Dissecting Aneurysm of the Aorta)

By HOWARD B. BURCHELL, M.D.

MEDICAL progress in the understanding of aortic dissection in vivo, commonly and improperly called "dissecting aneurysm," has been, in a schematic sense, mainly horizontal and not vertical. Charted to the left, one might note much progress in the alerting of medical students to the occurrence and general symptoms of this condition; charted to the right, one might note the expanded knowledge of the specialists concerning the associated background conditions and the unique symptom complexes. In the vertical ordinate, progress in regard to the probing of underlying basic causes would be noted to be limited; likewise, the ascent on the vertical scale as a reflection of specific prevention or treatment has been, indeed, of modest degree.

My own interest in this condition originated about a quarter of a century ago in medical school, where I was attracted by apparent paradoxes and controversies concerning the nature of the condition. I remember walking from one class where, in a historical preamble to a discussion of this disease, it was mentioned that King George II had died of it, to another class where it was mentioned that this king had died of cardiac rupture. Also, I was impressed with the strange fact that the aorta, which might withstand an intraluminal pressure of 3,000 mm. of mercury, could readily be split longitudinally, the latter phenomenon being demonstrated in the aortas of elderly subjects very dramatically by my professor, Dr. Oskar Klotz, by simply pulling the layers apart throughout the whole length of the aorta. In addition, it was evident that the name "dissecting aneurysm" was a misnomer—that the condition was rather a dissecting hematoma with progressive splitting of the medial layer. A controversy was also evident concerning the role that syphilis of the aorta might play; Dr. Klotz, in demonstrating the histologic lesion of chronic syphilis of the aorta, maintained that it would be protective against the dissecting intramedial force.

Keys and I[1] studied the necropsy report on King George II and concluded that the lesions of both myocardial rupture and aortic hematoma were present, although data were generally inadequate as to the pathogenesis of these lesions. Although it is now generally recognized that "dissecting aneurysm" is not an accurate term, it is probable that it will be slow to be erased from the medical literature; yet one should make a plea that it be so erased. I believe that now it will be universally conceded that syphilis is not etiologically related to "dissecting aneurysm" and that the lesions of chronic syphilis would prevent or limit aortic dissection.

INCIDENCE AND TYPES

There is evidence of an increasing incidence of aortic dissection, and perhaps this is largely related to an aging population. Kirkpatrick[2] found only 22 well-authenticated cases in the pathologic archives of the Mayo Clinic up to 1948, but since that time there have been nearly as many more, that is, 18 cases in the past seven years.

From the Section of Medicine, Mayo Clinic, Rochester, Minn.

A similar increase has been noted in other centers. For example, at the Massachusetts General Hospital, Glendy and associates[3] found records of 21 cases that had been encountered up to 1937, and David and co-workers[4] found records of 17 cases encountered in the 10-year period 1937 through 1946. Compared with myocardial infarction, aortic dissection is still a rare lesion, and a busy consulting cardiologist might practice for many months without seeing a case. While the healed form of dissection is well known to the pathologist, it is even rarer than the unhealed form, as an overwhelming majority of the cases that the pathologist sees are in an acute or subacute stage and have clinical histories that encompassed only hours or days. In the 40 necropsy cases available for study at the Mayo Clinic, the length of survival has generally been directly proportional to the distance of the intimal tear from the aortic valve, an observation that is far from new, as it was made by Peacock[5] in 1863. Outstanding exceptions are not rare; for example, there is the clinic patient with paraplegia who lived for five months without further circulatory trouble but whose intimal tear was in the ascending aorta. This case has been discussed in some detail by Moersch and Sayre.[6]

Over the years, the types of lesion have shown the same variegated pattern, and at the Mayo Clinic the anatomic distribution of the tears remains the same as that reported by Kirkpatrick[2] (fig. 1). The general pathologic problem may be introduced visually by reference to figures 2 and 3. Roughly, the primary intimal tear was in the ascending aorta in approximately 50 per cent of the cases, in the arch in 30 per cent and in the descending thoracic aorta in 20 per cent. In approximate percentages, the dissection involved the ascending aorta in 70 per cent, the arch in 90 per cent and the descending thoracic and the descending thoracic and abdominal aorta in 80 per cent. In the 22 cases the right and left coronary orifices were each involved twice, the innominate artery five times, the left carotid six times, the left subclavian eight times, the celiac axis and superior mesenteric each twice, the left renal artery nine times and the right twice, and the left iliac 12 times and the right nine times.

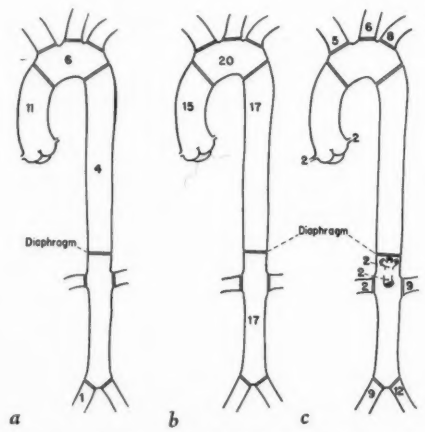


FIG. 1. Distribution of 22 Mayo Clinic cases of aortic dissection encountered prior to 1948 (Kirkpatrick[2]) according to sites of intimal tear and parts involved by dissection. *a*. Sites of intimal tear. *b*. Parts of aorta involved. *c*. Large aortic branches involved significantly.

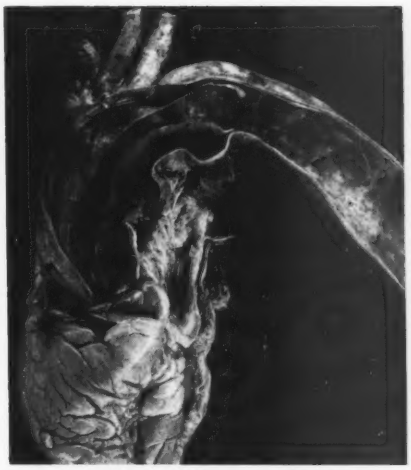


FIG. 2. Gross specimen showing extensive dissection of sheath of ascending portion and arch of aorta, with compression occlusion of innominate artery. The intimal tear may be seen just proximal to the origin of the innominate artery. The patient, a woman 79 years of age, had sudden syncope and presented as a problem of hemiplegia with associated aortic insufficiency. Death occurred three days after onset of illness and gross hemopericardium was present at postmortem examination. There was no adequate explanation for the diastolic bruit in the careful study of the aortic valve, which appeared normal and competent.

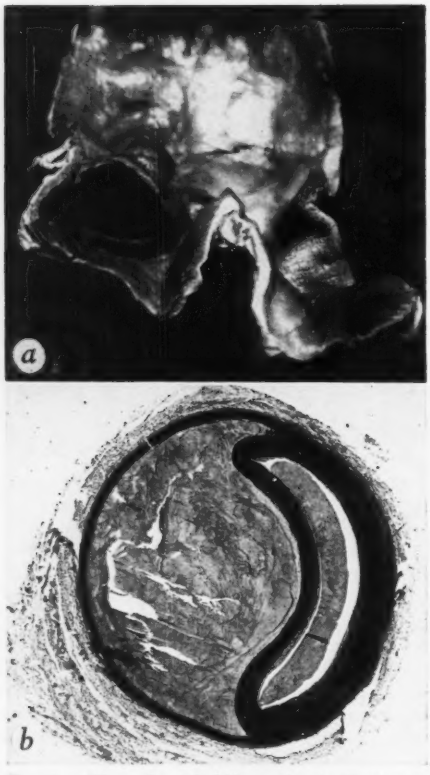


FIG. 3. *a*. View of aortic bifurcation to illustrate reentry tear into right internal iliac artery. *b*. Low-power view of cross section of subclavian artery to illustrate dissecting hematoma, in outer third of media, that obstructs original lumen (courtesy of Dr. J. E. Edwards).

ETIOLOGY

Although a detailed discussion of basic etiologic factors does not properly belong in a clinical progress report, certain problems need to be mentioned, as they bear directly on the clinical problem. The following categories of problems are mentioned.

1. *Experimental Problems.*

The occurrence of "spontaneous" aortic dissection and rupture in rats fed sweet-pea meal has created interest, whether it is to be related to a possible toxic factor or to a specific protein deficiency.[7] Rats fed aminonitriles also have experienced aortic rupture.[8]

2. *Physical Anthropologic Problems.*

The occurrence of dilatation of the great vessels of the heart and aortic rupture in association with Marfan's syndrome is generally recognized in the cardiologic world, and McKusick[9] has discussed this problem in detail in a recent review. Of perhaps novel interest is the evidence[10] that a localized abiotrophic trait may be carried in a family group containing persons with the complete Marfan syndrome and that some individuals of normal body habitus within such a group might have aortic dissection and rupture. Aortic dissection with a false aneurysm has been observed in association with marked funnel depressions of the thorax, and I have observed one such case, the presenting problem being that of left bronchial obstruction and atelectasis. Such an association must be rare, as Evans[11] mentioned none in his report on the heart in sternal depression.

3. *Systemic Problems.*

(1) *Pregnancy.* Throughout reports in the literature on aortic dissection and rupture, the not infrequent mention of the association of this condition with pregnancy is notable. In a review of 49 cases of aortic dissection in females, Schnitker and Bayer[12] found that 24 occurred in association with pregnancy. Just how the pregnant state is facilitative or permissive of aortic degeneration and medial splitting is not clear at the present time, although the typical lesion of idiopathic medionecrosis cystica may be seen.

(2) *Hypertension.* If Marfan's syndrome and pregnancy are excluded, it is proper to teach that aortic dissection is always associated with hypertension—"always" is a treacherous, tyrannical word and exceptions undoubtedly occur. As judged from the data reported from the Army Institute of Pathology by Gore and Siewert,[13] the younger the patients the larger is the number without evidence of hypertension. Not a few subjects to become the victims of this condition have had a history of recent hypertension of a severe progressive type. Although it is recognized that the marked elevation of blood pressure during the patient's

acute illness may not be representative of previous hypertension, it is notable that a considerable number of *our* cases have come from the group of patients with hypertensive retinopathy, that is, those with so-called malignant hypertension.

(3) *Coarctation.* In about 10 per cent of untreated patients with coarctation, aortic rupture with dissection and hemopericardium is the cause of death. The proximal aorta is usually the location of the dissection, but in rare instances the aorta distal to the coarctation may also be the site of dissection.

(4) *Aortic Valvular Disease.* Aortic dissection may occur with chronic aortic valvular disease particularly if the latter is of moderate degree, but the two conditions occur together so rarely that a cause-and-effect relationship seems unlikely.

(5) *Myxedema (?).* Kountz and Hempelmann[14] reported three cases of aortic dissection that had followed thyroidectomy; although they considered the possibility of coincidence, they deemed it proper to infer a causal relationship. It does seem that the relationship may have been coincidental, as Blumgart,[15] in his own cases of total thyroidectomy and I^{131} treatment, has not observed this complication, nor has he learned of cases in other centers utilizing I^{131} in the therapy of heart disease. It has not occurred in my experience. A few of the patients at the Mayo Clinic had been on potassium sulfocyanate therapy but no causal relationship could possibly be implied.

4. *Histologic Problems.*

Medial degeneration may be accepted as a sine qua non of spontaneous aortic dissection, and the form described by Erdheim under the term "medionecrosis cystica" is often encountered in various degrees of its classic advanced state. It seems plausible to claim that this histologic picture does not represent a specific disease process but rather a metabolic end-effect to which the hypertension in some way may strongly contribute. In young adults the degenerative medial change is described by Gore[13] to be mainly degeneration of the elastica. Readers are referred to pathologic theses on this subject but may be disappointed in the lack of basic knowledge concerning the pathogenesis of the degenerative medial lesions.

Atherosclerosis is not to be regarded as a cause of aortic dissection, although dissection may occur in atherosclerotic aortas. In rare cases, as exceptions to the rule, an aortic split may originate in the base or edge of an atheromatous plaque. In Shennan's[16] large series of 218 cases, an atherosclerotic lesion was the site of intimal rupture in about 2.5 per cent. Syphilis has already been mentioned as not being etiologically related, and in those cases in which both an aortic dissection and a syphilitic lesion are present, the two conditions are not mingled. The case reported by Weiss[17] deserves special mention in that there was a large, saccular, aortic aneurysm and an aortic dissection, and one of the main points of the discussion concerned the absence of any overlapping of the syphilitic and dissected areas of the aorta. The view that the aneurysm was syphilitic should not remain unchallenged, however, despite the patient's positive Wassermann reaction, as the lesion occurred in the characteristic area for traumatic rupture or partial dissection with a false aneurysmal sac, and the ascending aorta showed no signs of a syphilitic process.

In rare instances, dissection may begin in the depth of a mycotic aneurysm as is illustrated by the well-documented case of subacute aortic bacterial endocarditis reported by Bartol and associates.[18] An instance of aortic dissection occurring with diffuse granulomatous aortitis has been reported by McMillan.[19]

5. *Dynamics.*

A sufficient number of cases of aortic hematoma without intimal rupture have been observed to give credence to the supposition that *all* dissecting hematomas begin with hemorrhage from vasa vasorum and that an intimal break is secondary. However, one still cannot help being attracted by the hypothesis that the lesion in some cases might be caused by the sudden longitudinal or circular stretching of the media with resultant partial separation of it and secondary intimal rupture, produced in the

proximal aorta by forces related to the stroke output of the heart. The not uncommon onset of the dissection subsequent to a bowel movement, which is a natural Valsalva procedure following which it is known that very large compensatory stroke volumes and high peripheral resistances are simultaneously present, may be cited as in some support of this thesis. The orientation of the intimal tear gives rather little help in the problem of dynamics. Usually, the tear has been thought of as being transverse, but many varieties of tears have been seen, with longitudinal tears apparently being particularly more common in young male groups.[13]

Exertion as a contributing cause cannot be established, since only in occasional cases has the onset of the dissection, as judged from the histories, occurred while the subject was exerting himself. Although Cherry and Cherry[20] discounted the possibility of exertion as a significant etiologic factor, moderate or heavy exertion was concomitant with the onset of the illness in 15 per cent of the 77 cases they reviewed. In one State, the court ruled[21] in favor of the plaintiff when an apparent aortic dissection occurred during his work. Whether or not partial forms of Marfan's abiotrophy might exist among the young, tall basketball players in this country is a provocative thought, and an occasional sudden death in such athletes following a game has been noted in the newspapers. Emotional storms coincident with the onset of illness have been reported in a small percentage of cases (described early by Peacock as associated with a "fit of passion"), and a causal precipitating relationship is probable.

General trauma related to sudden deceleration or compression of the intrathoracic parts may be considered a possible initiating factor but no convincing evidence is available to support this speculation. There is a form of traumatic aneurysm of the aortic arch (in the form of aortic rupture, hematoma and false aneurysm), and it is possible that such lesions could be complicated by medial dissection in rare cases. One of the cases at the clinic may represent such a sequence of events, since a severe injury of the thorax occurred in an automobile accident six months before the acute illness. There are reports of other similar cases in the literature.

Clinical Picture

The clinical picture resulting from aortic dissection is extremely and characteristically protean, and such wide variety should be expected in view of the varied parts of the aorta that may be involved and the varied tissues that may bear the brunt of the secondary trauma, either through direct destruction or ischemia. The clinical picture varies with time, and sometimes distinct phases are recognized, that is, phase of onset, phase of progression, phase of complications and phase of death or of recovery with sequelae. However, the whole process in all its phases may be over in a matter of moments, and the lesion is the cause of death in a considerable proportion of coroners' cases of sudden death. As a clinical problem, however, there is characteristically the history of severe unrelenting pain, which "marches" from one region to another, particularly from thorax to back, to abdomen, to extremities. Pain may occur in the face, ear or neck before it is felt elsewhere. Pain may be absent, particularly when cerebral arterial insufficiency has occurred early in the attack.

The onset is not infrequently associated with syncope or shock. Characteristically, however, when the patient is admitted, the blood pressure may be found to be very high—pressures of 250 mm. of Hg systolic and 150 diastolic not being unusual—despite the fact that he may be cold and sweaty and have a feeble pulse. One may hear a double bruit at the aortic area, and this may be a transient or, more often, a persistent phenomenon. Arterial pulsations may or may not be unequal in arteries of the extremities. Neurologic conditions, particularly paraplegia or hemiplegia, may be the main features, or abdominal symptoms may be predominant with pain, distention and urge to defecation. Acute pancreatitis or mesenteric thrombosis may be suspected. Usually, however, myocardial infarction is the condition most often suspected in problem cases; it is particularly logical to suspect myocardial infarction when the patient previously has had anginal pain or even myocardial infarction and then experi-

ences a new attack of severe thoracic pain which often is the presenting complaint in aortic dissection.

Hoarseness has been known to occur; assumedly, it is related to paralysis of the left vocal cord through involvement of the left recurrent laryngeal nerve. Rarely, Horner's syndrome also may be seen.

Fever and leukocytosis may occur early. If external bleeding is occurring, progressive anemia may be noted. On rare occasions, there may be ecchymosis of the upper part of the thorax and lower part of the neck. In one such case,[22] the patient survived a year, after which the site of external aortic rupture could not be identified by the pathologist.

Diagnosis

If it is possible to obtain a clear history of severe pain that migrates according to progressive dissection of the aortic length and to observe the patient to have an accession to a severe hypertension and to have inequality of the pulses in the peripheral vessels, then it is proper to make the diagnosis of aortic dissection. Further corroboration may come from an electrocardiogram which may show either a normal condition or evidence only of left ventricular hypertrophy, and from a roentgenogram which shows widening of the superior mediastinal shadow or definite dilatation of the aorta and perhaps fluid (blood) in the left pleural cavity. In such a case the lesion would be easily recognized, but in other cases in the acute phases of the disease the patient may, at the onset, present hemiplegia or paraplegia, manifestations of an acute abdominal catastrophe or evidence of renal insufficiency in the form of acute oliguria.

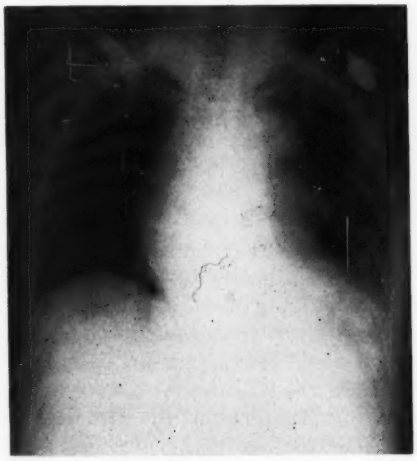


Fig. 4. Roentgenogram of chest of a woman aged 56 years who died 24 hours after onset of severe substernal pain. She had been under therapy for hypertension at the clinic for 20 years and had presented a normal aortic shadow in the previous roentgenograms. An aortic diastolic murmur was heard, and there was evidence of cerebral ischemia. Death was related primarily to extensive dissecting hematoma and to hemopericardium.

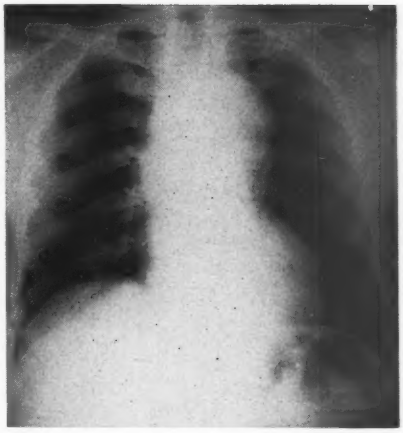


Fig. 5. Roentgenogram of chest of a man aged 39 years who died 11 days after onset of acute illness ushered in by severe interscapular pain. The blood pressure was 250/190. Convulsions and abdominal pain characterized the latter part of the illness. Death was sudden. At postmortem examination the intimal tear was found just distal to the ligamentum arteriosum and there was massive hemothorax on the left.

Despite the slight macabre hue to the story, it may be mentioned that James Paullin, a long-time student of the problem of aortic dissection, died with this condition, diagnosing it with accuracy, insisting he could feel his aorta tearing, and correctly predicting that rupture would take place into the left pleural cavity.[23]

If the patient recovers from the acute phases of his disease, he may return to the hospital months later because of heart failure attribut-

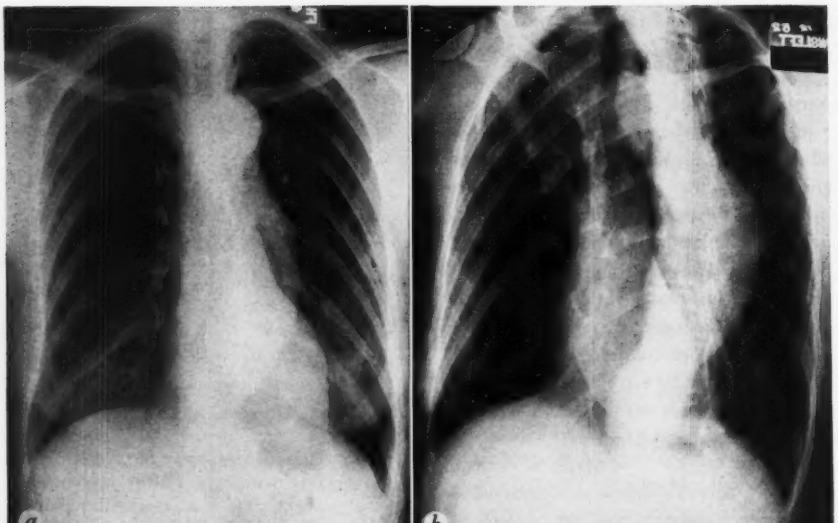


FIG. 6. *a* and *b*. Anteroposterior and left oblique roentgenograms of the chest of a woman aged 32, in 1951, who gave a history that in the last month of pregnancy she experienced severe substernal and back pain that was not alleviated by morphine. Delivery of a live baby occurred two and one-half hours later but the patient was unaware of labor pains. The postpartum course was complicated by heart failure which responded to therapy. The blood pressure was 150/80. The home physician reported that the patient was still living in May, 1955, that she was doing her own housework and that the roentgenographic appearance of the thorax was not essentially different from that of 1952 as shown here.

able perhaps by the clinician to the hypertension or possibly to syphilitic or rheumatic aortic valvular disease.[24, 25] Also, the patient may have bizarre pains that take him to the neurologist, or he may have unusual abdominal or thoracic complaints that take him to the internist.

The roentgenologic picture may be exceedingly helpful, and little has been added to knowledge in this field since the study of Wood and associates.[26] In the chronic or healed stage of the disease, the location of the main lesion may be suspected but usually the whole aortic shadow is diffusely enlarged. Characteristic roentgenograms are shown in figures 4, 5 and 6. The aorta in this disease has been outlined very well by angiocardiography,[27] but the usually benign reactions to this procedure might be more feared in patients with an acute aortic dissection.

DIFFERENTIAL DIAGNOSIS

Few, if any, cardiologists have not been perplexed by the symptoms of aortic dissection or have not held clinics on the victims of this condition. The ease of diagnosis has been stressed by some. For example, Middleton[28] stated that the prediction that junior medical students should soon be making the diagnosis with ease was "not stretching the issue too far." One result has been that the diagnosis is suggested in most cases of thoracic pain and, hence, false-positive diagnoses may not be infrequent. When the necropsy protocol is read, it is usually very evident why the symptoms occurred, but in the hospital the majority of instances are still difficult to diagnose without considering alternate explanations of the symptom complex. While the last 10 Mayo Clinic patients who have had aortic dissection and have lived more than a day have had the diagnosis suggested, the notes did not reflect such self-assurance in the correctness of the diagnosis as is usually evident in the notes pertaining to the diagnosis of acute myocardial infarction.

Hypertensive and coronary arteriosclerotic disease is first on the list for differential diagnosis. Patients in whom these conditions have

been the main problem, perhaps with proved myocardial infarctions in the past, may have aortic dissection as a terminal event. A patient with myocardial infarction may have embolic episodes of such a nature as to suggest arterial occlusion by dissection. Cerebral arterial insufficiency in association with acute myocardial infarction may not be of embolic origin but, as emphasized and documented by Bean and associates,[29] acute myocardial infarction at its debut may "masquerade" as an acute cerebral disturbance such as hemiplegia. The dynamic background of such a syndrome is believed to be a hypotensive state at the onset of the infarction. Death from acute myocardial infarction is attributable to rupture of the heart in approximately 15 per cent of all fatalities, and since this frequently occurs in elderly women in whom the blood pressure remains elevated, aortic dissection might well have been considered clinically. Particularly would this be true if one did not have good electrocardiographic evidence of the infarction. A further obstacle to diagnosis is the fact that the lateral wall of the heart may be the site of infarction and rupture, so that the electrocardiogram may not be definitive of the diagnosis.

The problem of differentiating aortic dissection from myocardial infarction may be further complicated by the fact that aortic dissection may involve the orifices of the coronary arteries and cause myocardial ischemia or infarction. While electrocardiographic tracings characteristic of infarction may be obtained in aortic dissection, only rarely do the changes follow a characteristic pattern. One of the best examples of an electrocardiogram, showing a typical posterior-infarct pattern following aortic dissection and coronary-artery obstruction, may be seen in the article of Levinson and associates.[30] It is of casual diagnostic interest that the electrocardiographic changes related to ischemic changes of the posterior wall might bring up the question of pulmonary embolism and acute cor pulmonale.

In its chronic phases, aortic dissection may present a difficult problem and a dilated atherosclerotic thoracic aorta combined with an atherosclerotic abdominal aneurysm of a leaking variety may suggest aortic dissection. Other causes of absent femoral pulses or unequal radial pulses, or both, require mention; these include coarctation with a subclavian artery that arises below the coarctation or is strictured at its orifice, and occlusive disease of aortic-arch branches that is associated with atherosclerosis or other types of arterial disease. Differential diagnosis in the presence of this problem has been discussed in a clinicopathologic conference by Barker and Edwards,[31] and a very full historical and clinical review of the "aortic arch syndromes" was published by Ross and McKusick.[32]

Although peripheral arterial occlusion, partial or complete, as illustrated in figure 3, has been properly emphasized as an important sign, it is remarkable that in many cases the pulses have been carefully noted to be normal.

In one case of coarctation of the aorta at the Mayo Clinic, the presenting symptom was sudden paraplegia and, as it is known that the anterior spinal artery acts as a collateral vessel in coarctation and hence is large and tortuous, a diagnosis of thrombosis of the anterior spinal artery was made. One lesion considered in the differential diagnosis was aortic dissection, but absence of pain was against this diagnosis. At the time of successful surgical repair of the coarctation some months later, no evidence of any abnormality except the typical coarctation was present, which is supportive also of the original diagnosis. No further signs relative to the spinal cord developed.

One patient at this clinic who presented a syndrome of migrating, severe pain and finally paraplegia and whose disease was tentatively diagnosed as aortic dissection was found at postmortem examination to have hematomyelia.[33] An interesting case of paradoxic emboli giving a clinical picture suggestive of dissecting aneurysm is reported in the clinicopathologic conferences of the Massachusetts General Hospital.[34] When acute aortic valvular incompetence is a predominant clinical sign of aortic dissection, then rupture of an aortic cusp or of an aortic-sinus aneurysm might need to be considered in the differential diagnosis.

Diagnosis of Site of Lesion

It is not enough to suspect a dissecting aneurysm or even to diagnose it; one should attempt to appraise its extent and the site of

TABLE 1. *Relation of Site of Intimal Tear to Site of Initial Pain**

Site of intimal tear	Total cases	Site of initial pain		
		Substernal	Back	Upper abdomen
Ascending aorta	32	19	4	9
Aortic arch	22	7†	7†	11†
Descending aorta	22	6	12‡	8‡
Total	76	32	23	28

* Based on selected cases in which the pain syndrome was well described, as follows: Mayo Clinic 18 cases, Holland and Bayley[35] 15 cases, Glendy and associates[3] 10 cases, Palmer and Mathison[36] 9 cases, Logue[37] 9 cases, Ritvo and Votta[38] 8 cases, Weiss[39] 5 cases and Bay[40] 2 cases.

† Three patients had pain simultaneously in front and back.

‡ Four patients had pain simultaneously in front and back.

the intimal tear. The latter may become increasingly important with the progress of surgical therapy. The site of initial pain may give a clue to the site of rupture, but correlation is not sufficiently good for it to be of real help (table 1). It would seem that if a patient lives long enough to reach a physician and gives an accurate history of back pain that often almost simultaneously is felt in the epigastrium, the chances favor the aortic arch or the portion of the aorta just beyond the left subclavian artery as the site of dissection. The location of the tear within the circumference of the media may often be inferred from the symptoms, as discussed in a later section of the paper.

If a pronounced and persistent murmur of aortic insufficiency has appeared, the likelihood that the intimal tear is within a few centimeters of the aortic valve is excellent. In chronic cases, the roentgenologist may be of great help in assessing the limits of the lesion.

RELATIONSHIP OF SYMPTOMS AND SIGNS TO PATHOLOGIC ANATOMY

Cases of dissection of the aorta usually are excellent problems for clinicopathologic conferences, as the symptoms and signs produce a tantalizing trail of events leading, with the usual distracting factors, toward the diagnosis, and pathologic events can usually be reconstructed so as to explain the clinical events.

In respect to the neurologic signs, hemiplegia may be explained on the basis of occlusion caused by dissection that extends into the innominate or contralateral carotid artery. Contralateral hemiplegia resulting from carotid occlusion may be associated in the characteristic way with homolateral retinal blindness. Paraplegia is related to dissection away from both of the pair of intercostal arteries which supplement the blood flow of the cord. Transient symptoms related to the cord have been explained by Moersch and Sayre[6] on the basis of first a compression of the intercostals within the aortic media by the dissecting hematoma and then a restitution of flow when the intercostal orifice separates from its original internal site and connects to the false channel. Edwards[41] has expressed the opinion that the frequent escape of the cord from ischemic damage is related to the usual left-sided location of the dissection in the aortic circumference so that the right intercostal and lumbar arteries are spared. This lateralized location of the dissection is reflected in the frequency of infarction of the left kidney as compared with the right, and in the occasional case in which there is ischemic pain in the left testicle but not in the right.

The disappearance and reappearance of pulsations in one or both femoral arteries may be explained on the basis of a re-entry break into the original aortic or iliac arterial lumen, and this chain of events is usually substantiated by the eventual pathologic examination.

Although the hypertension with which aortic dissection is associated is usually of long standing, the very high blood pressures that exist at the time of the acute illness lend credence to the hypothesis that in some cases an added factor of renal hypertension (ischemic kidney) may be operative. It cannot be gainsaid also that dissection of the aortic arch, together with involvement of branches of the aortic arch, could destroy the depressor nerve mechanism so that a transient reflex neurogenic hypertension could be added. Also, in other cases, the relative ischemia of the whole brain and medulla could be a factor in the hypertension.

A frequent and characteristic sign that may appear in dissecting aneurysm is a double ("to-and-fro") aortic murmur. It may be related to aortic insufficiency when the aorta is practically avulsed from the heart and the aortic valve tends to be invaginated into the ventricle with each diastole, as occurred in one of the cases illustrated by Klotz and Simpson.[42] In most cases, however, the tear is incomplete and, although one cannot reconstruct the dynamics of the aortic insufficiency with dogmatic self-assurance, the mechanism of loosening of one of the commissures as discussed in detail for partial dissections by Peery[24] is a favored one. Levinson and associates[30] found no evidence of a dilated valve ring. The thesis of a flow of blood into and out of the hematoma, originally promulgated by Resnik and Keefer,[43] perhaps would serve to explain a case in which the dissection is considerably removed from the aortic area. The observation of a unilateral double carotid pulse in one case by Nissim[44] may be quoted in support of the viewpoint that the hematoma acts as a systolic reservoir where murmurs may occur as blood enters and leaves the reservoir.

Pericarditis has been observed, and it occurred in one of the Mayo Clinic cases. It is best explained as a result of slight suffusion of blood into the pericardium. Coronary insufficiency may occur, as previously related, from involvement of the coronary orifices.

Treatment

In standard texts, treatment has often been dismissed with a sentence or so to the effect that the patient should be kept at rest and made comfortable with narcotics. For those patients who recover from the initial onslaught of the dissection, it is believed rational to treat them with the ganglion-blocking antihypertensive agents, and my colleagues and I have done this with indifferent success. Anticoagulants are believed to be contraindicated because of the danger of facilitating any leak that may be occurring at the site of an almost-accomplished external rupture; it is doubtful if they would have any influence on progression of the dissection per se. One case in which anticoagulants were given on the basis of a mistaken diagnosis of myocardial infarction has been reported by Brumfitt.[45]

Surgical relief of an ischemic limb by creation of a re-entry opening in the dissected femoral artery was reported by Gurin and associates.[46] Apparently the first to make a frontal attack on the lesion itself, according to Paullin and James,[47] was Osler Abbott, who wrapped the area of involved aorta with cellophane. The two patients who were operated upon are known to have lived more than two years but have been lost to follow-up at the present time. Abbott[23] expresses no convictions concerning the established worth of the procedure of cellophane wrapping and thinks that perhaps, ideally, early surgical treatment with replacement by graft of a limited aortic dissection might be carried out in selected cases. He also feels that there is a major value in using a Blalock type everting suture for anastomosis in aortas prone to dissection. De Bakey[48] has had successful results, in four of six patients operated upon, by carrying out a type of plastic repair on the aorta whereby the aorta is transected, the distal split rejoined and the aorta reconstructed. The ultimate results will need further survey. The problem will arise as to whether exploration should be performed as an emergency following the tentative diagnosis when the patient is first seen by the physician, or whether it is only for the chronic form of the disease that surgical measures should be recommended. Emergency surgical repair was carried out in one of the cases reported by De Bakey. The patient had a murmur of aortic insufficiency, and death was attributable to hemopericardium. It seems likely, at this time, that the early appearance of cerebral infarction or severe aortic insufficiency, signifying both the proximal location of the affected portion of the aorta and the limitations of surgical salvage, would be a relative contraindication to emergency surgical efforts. A mild optimism may be entertained concerning this avenue of therapeutic endeavor and this view is apparently shared by Baer,[49] who recently reviewed the problem.

Epilogue

Engendered as a simple report on clinical progress in respect to dissection of the aortic

media, this paper has metamorphosed into a general brief review of the problem. In the latter form, it suffers from lack of detail concerning the clinical picture and from lack of reference to many excellent papers. As one reads numerous case reports in sequence, one encounters recurring familiar themes, but each report usually has intriguing variations to set it apart a little from the others, so that no absolutely stereotyped or routine clinical picture can be found to exist. Probably, cases of dissecting aneurysm will continue to be frequent selections for clinical conferences, and at the present time the trend may be to suspect it more frequently than the clinical data may warrant.

Most advance has probably been made in the understanding of the pathogenesis and significance of incompetence of the aortic valve and in the understanding of the neurologic complications and the roentgenologic findings. The attack on the lesion by surgeons gives considerable promise, particularly, if the lesion is in the distal part of the aortic arch or in the descending thoracic aorta.

REFERENCES

[1] Burchell, H. B. and Keys, T. E.: The heart of George II of England. Bull. M. Library A. **30:** 198, 1942.

[2] Kirkpatrick, N.: Dissecting Aneurysm of the Aorta. Thesis, Graduate School, University of Minnesota, 1949.

[3] Glendy, R. E., Castleman, B. and White, P. D.: Dissecting aneurysm of the aorta: A clinical and anatomical analysis of nineteen cases (thirteen acute) with notes on the differential diagnosis. Am. Heart J. **13:** 129, 1937.

[4] David, P., McPeak, E. M., Vivas-Salas, E. and White, P. D.: Dissecting aneurysm of aorta: A review of 17 autopsied cases of acute dissecting aneurysm of the aorta encountered at the Massachusetts General Hospital from 1937 to 1946 inclusive, eight of which were correctly diagnosed ante mortem. Ann. Int. Med. **27:** 405, 1947.

[5] Peacock, T. B.: Report on cases of dissecting aneurism. Tr. Path. Soc., London **14:** 87, 1863.

[6] Moersch, F. P. and Sayre, G. P.: Neurologic manifestations associated with dissecting aneurysm of the aorta. J.A.M.A. **144:** 1141, 1950.

[7] Bachhuber, T. E. and Lalich, J. J.: Production of dissecting aneurysms in rats fed lathyrus odoratus. Science **120:** 712, 1954.

[8] Wawzonek, S., Ponseti, I. V., Shepard, R. S. and Wiedenmann, L. G.: Epiphyseal plate lesions, degenerative arthritis, and dissecting aneurysm of the aorta produced by aminonitriles. Science **121:** 63, 1955.

[9] McKusick, V. A.: The cardiovascular aspects of Marfan's syndrome: A heritable disorder of connective tissue. Circulation **11:** 321, 1955.

[10] Whittaker, S. R. F. and Sheehan, J. D.: Dissecting aortic aneurysm in Marfan's syndrome. Lancet **2:** 791, 1954.

[11] Evans, W.: The heart in sternal depression. Brit. Heart J. **8:** 162, 1946.

[12] Schnitker, M. A. and Bayer, C. A.: Dissecting aneurysm of the aorta in young individuals, particularly in association with pregnancy: With report of a case. Ann. Int. Med. **20:** 486, 1944.

[13] Gore, I., and Siewert, V. J.: Dissecting aneurysm of the aorta: Pathologic aspects; an analysis of eighty-five fatal cases. Arch. Path. **53:** 121, 1952.

[14] Kountz, W. B. and Hempelmann, L. H.: Chromatrophic degeneration and rupture of the aorta following thyroidectomy in cases of hypertension. Am. Heart J. **20:** 599, 1940.

[15] Blumgart, H. L.: Personal communication to the author.

[16] Shennan, T.: Dissecting aneurysms. Medical Research Council Special Report Series, No. 193. London, His Majesty's Stationery Office, 1934.

[17] Weiss, S.: Dissecting aneurysm of the aorta: Two cases with unusual features. New England J. Med., **218:** 512, 1938.

[18] Bartol, G. M., Edwards, J. E. and Lamb, M. E.: Mycotic and dissecting aneurysms of the aorta complicating bacterial endocarditis. Arch. Path. **35:** 285, 1943.

[19] McMillan, G. C.: Diffuse granulomatous aortitis with giant cells associated with partial rupture and dissection of the aorta. Arch. Path. **49:** 63, 1950.

[20] Cherry, C. B. and Cherry, K. T.: Dissecting aneurysm of the aorta: Evaluation of the role of exertion in its production. Indust. Med. **10:** 525, 1941.

[21] Medicolegal: Aortic aneurysm and cerebral embolism due to accident. J.A.M.A. **94:** 1529, 1930.

[22] Thomson, A. P. and Marson, F. G. W.: Dissecting aneurysm of the aorta. Lancet **1:** 482, 1955.

[23] Abbott, O.: Personal communication to the author.

[24] Peery, T. M.: Incomplete rupture of the aorta: A heretofore unrecognized stage of dissecting aneurysm and a cause of cardiac pain and cardiac murmurs. Arch. Int. Med. **70:** 689, 1942.

[25] Levine, E., Stein, M., Gordon, G. and Mitchell, N.: Chronic dissecting aneurysm of the aorta

resembling chronic rheumatic heart disease. New England J. Med. **244:** 902, 1951.

[26] Wood, F. C., Pendergrass, E. P. and Ostrum, H. W.: Dissecting aneurysm of the aorta: With special reference to its roentgenographic features. Am. J. Roentgenol. **28:** 437, 1932.

[27] Golden, A. and Weens, H. S.: The diagnosis of dissecting aneurysm of the aorta by angiocardiography: Report of a case. Am. Heart J. **37:** 114, 1949.

[28] Middleton, W. S. and Porter, R. R.: The diagnosis of spontaneous dissecting aneurysm of the aorta. Tr. A. Am. Physicians **52:** 67, 1937.

[29] Bean, W. B., Flamm, G. W., and Sapadin, A.: Hemiplegia attending acute myocardial infarction. Am. J. Med. **7:** 765, 1949.

[30] Levinson, D. C., Edmeades, D. T. and Griffith, G. C.: Dissecting aneurysm of the aorta: Its clinical, electrocardiographic, and laboratory features; a report of fifty-eight autopsied cases. Circulation **1:** 360, 1950.

[31] Barker, N. W. and Edwards, J. E.: Primary arteritis of the aortic arch. Circulation **11:** 486, 1955.

[32] Ross, R. S. and McKusick, V. A.: Aortic arch syndromes: Diminished or absent pulses in arteries arising from arch of aorta. Arch. Int. Med. **92:** 701, 1953.

[33] Brandenburg, R. O. and Sayre, G.: Unpublished data.

[34] Case Records of the Massachusetts General Hospital: Case 22212: Presentation of case. New England J. Med. **214:** 1052, 1936.

[35] Holland, L. F. and Bayley, R. H.: Dissecting aneurysm: A report of nineteen cases, with a review of the recent American literature. Am. Heart J. **20:** 223, 1940.

[36] Palmer, J. D. and Mathison, A. K.: Dissecting aneurysm of the aorta (a study of a series of fourteen cases). Canad. M. A. J. **55:** 585, 1946.

[37] Logue, R. B.: Dissecting aneurysm of the aorta. Am. J. M. Sc. **206:** 54, 1943.

[38] Ritvo, M. and Votta, P. J.: Clinical and roentgen manifestations of dissecting aneurysm of the aorta. Am. J. Roentgenol. **52:** 583, 1944.

[39] Weiss, S.: The clinical course of spontaneous dissecting aneurysm of the aorta. M. Clin. North America **18:** 1117, 1935.

[40] Bay, E. B.: Dissecting aneurysm of the aorta. M. Clin. North America **28:** 112, 1944.

[41] Edwards, J. E.: Personal communication to the author.

[42] Klotz, O. and Simpson, W.: Spontaneous rupture of the aorta. Am. J. M. Sc., **184:** 455, 1932.

[43] Resnik, W. H. and Keefer, C. S.: Dissecting aneurysm with signs of aortic insufficiency: Report of a case in which the aortic valves were normal. J.A.M.A., **85:** 422, 1925.

[44] Nissim, J. A.: Dissecting aneurysm of the aorta: A new sign. Brit. Heart J. **8:** 203, 1946.

[45] Brumfitt, W.: An unusual case of dissecting aneurysm of the aorta. Lancet **2:** 792, 1954.

[46] Gurin, D., Bulmer, J. W. and Derby, R.: Dissecting aneurysm of the aorta: Diagnosis and operative relief of acute arterial obstruction due to this cause. New York J. Med. **35:** 1200, 1935.

[47] Paullin, J. E. and James, D. F.: Dissecting aneurysm of aorta. Postgrad. Med. **4:** 291, 1948.

[48] De Bakey, M.: Read at the meeting of the American Surgical Association, Philadelphia, Pennsylvania, April 27 to 29, 1955; also personal communication to the author.

[49] Baer, S.: Dissecting aneurysm of the aorta. Mod. Concepts Cardiovas. Dis. **23:** 214, 1954.

CLINICAL PROGRESS

EDITOR: HERRMAN L. BLUMGART, M.D.

ASSOCIATE EDITOR: A. STONE FREEDBERG, M.D.

Unusual Manifestations of Coarctation of the Aorta

By GEORGE C. GRIFFITH, M.D., ROBERT W. OBLATH, M.D. AND JOHN C. JONES, M.D.

COARCTATION of the aorta often is associated with other lesions or defects of the heart or great vessels which may influence the outcome of surgery. Infrequently, the coarctation occurs at an atypical site. Of the 118 cases to be reviewed in this paper, 56, or, roughly, one in two, present unusual findings. The frequency with which complicating conditions are met makes the search for additional pathology mandatory when surgical correction of the coarctation is under consideration.

METHOD USED IN SELECTING CASES

The case reports, physical findings, operative reports and postmortem findings of patients with coarctation seen at several Los Angeles hospitals were reviewed carefully. Cases in which only scanty information was available were discarded as unsuitable for the purposes of this study. There were 118 cases where the description of the coarctation and associated pathology was deemed adequate. In 56 instances, the condition was complicated by the presence of one or more additional defects.

CLASSIC SYMPTOMS OF COARCTATION

Most cases of heart failure in the acyanotic infant under 6 weeks of age are traceable to the infantile type of coarctation or aortic stenosis. The adult type of coarctation, in which the constriction is usually limited to a small segment of the aorta, is seen more commonly by the clinician. Evidences of the adult type of coarctation include: (1) reduced or absent pulsations in the abdominal aorta and femoral arteries, associated with hypertension in the upper limbs; (2) a fairly loud, rough, precordial systolic murmur of maximal intensity over the base of the heart, occurring a short but perceptible time after the first heart sound and not accompanied by a palpable thrill at the base of the heart: if the coarctation is complete the murmur may be absent; (3) collateral arterial circulation, evidenced radiographically by enlargement of the vessels in the superior mediastinum and/or upon auscultation, by bruits over the enlarged intercostal arteries and branches of the internal mammary arteries; (4) other evidence of aortic blocking, such as hypertrophy of the left ventricle and dilatation of the ascending aorta; (5) a defect or break in the continuity of the aortic outline in the left anterior oblique position, visualized either at fluoroscopy or on roentgenograms; (6) absence of the aortic knob, normally visible to the left of the spine at the level of the fifth dorsal vertebra in the adult; (7) bilateral notching (erosion) of lateral and posterior portions of the ribs; (8) abnormal asynchronism between the radial and femoral arteries: in a patient with aortic coarctation, the onset of the upstroke and the summit of the pulse wave are earlier in the radial than in the femoral artery where normally, the reverse is true;[1] (9) a notch in the left border of the descending aorta, just at the level of the left main pulmonary artery[2] and (10) significant diastolic vibrations reported in

From the Department of Medicine (Cardiology), University of Southern California School of Medicine and the Los Angeles County Hospital, Los Angeles, Calif.

Presented at the Annual Meeting of the American Medical Association, New York City, June 4, 1953.

phonographic tracings from the dorsal spine of patients with coarctation of the aorta.[3]

Unusual Findings on Physical Examination

Diminished or absent radial pulse on one side: In coarctation of the adult type, the stenotic portion of the aorta usually lies in the vicinity of the ductus arteriosus, most often just beyond the origin of the left subclavian artery; however, coarcted areas have been found both proximal and considerably distal to this site. Absence of the left carotid and left subclavian pulses, or reduced pulsation in these vessels, suggests a coarctation situated between the origins of these vessels.

At times the coarctation is limited to the left subclavian artery alone. Such a localized coarctation may cause no symptoms whatsoever, save for an absent or diminished left radial pulse and, possibly, hypertension in the right arm. However, absence of the left radial pulse may be caused by a number of factors, such as a large cervical rib, an aortic aneurysm, or a tumor compressing the left subclavian artery.[4] These and other more common conditions should be ruled out before a diagnosis of coarctation of the left subclavian artery is hazarded.

Unilateral rib notching: Unilateral rib notching on the right side of the body furnishes confirmatory evidence of a coarctation between the origins of the left carotid and left subclavian arteries, demonstrating that the right subclavian artery and its branches have assumed the brunt of collateral function.

If, on the other hand, the coarctation were less typically situated and had encroached upon the origin of the right subclavian artery, the left subclavian artery and its branches would be utilized to bypass the coarcted or atresic area, and this fact might be mirrored in unilateral rib notching on the left side of the body.

Infrequently, obliteration of the left subclavian artery results in unilateral rib notching.

Pulsations below the diaphragm: Absence of abdominal aortic pulsation and presence of the propulsion pulse in the femoral arteries suggests an atresia of the distal aorta. When the coarctation occurs below the diaphragm, it is usually located at or below the renal arteries.

Visualization of the Coarctation

Routine clinical methods are inadequate for the accurate localization of the level of aortic obstruction. Although, in the great majority of cases, the coarctation may be assumed to lie at or near the ductus arteriosus, the occasional occurrence of the constriction at other sites makes imperative accurate localization of the obstruction. In at least one instance, two areas of coarctation have been present in the same patient.[5]

Visualization of the constriction may be facilitated by means of angiocardiography or, preferably, by aortography. Occasionally, the coarcted area is visible in the left oblique position against a barium-filled esophagus. In addition to providing information concerning the degree of coarctation and the level at which the obstruction has occurred, accurate visualization of the constriction provides information concerning the length of the stenotic area and permits estimation of the distance between the orifice of the left subclavian artery and the site of the constriction; important factors in determining the feasibility of surgical correction.

Findings in the Established Cases (118) of Coarctation

Coarctation as sole defect: Surgical Correction Performed: Sixty-two patients, 46 males and 16 females, with coarctation uncomplicated by other defects and all evidencing classic symptoms of coarctation were operated upon without incident. The youngest in the group was two and one-half years old, the eldest, 49.

Coarctation complicated by other defects: Patients who survived operation. Eighteen patients survived operation for surgical correction of the coarctation in spite of complicating factors. In nine of these patients, the complicating condition was a patent ductus arteriosus. Descriptions of pathology found at operation may be found in table 1.

Exploration without surgical correction: Exploration was performed but no surgical correction was attempted in seven cases. In two

TABLE 1.—*Coarctation Complicated by Other Defects: Findings in Patients Who Survived Operation*

Findings	No. of Cases
Patent ductus arteriosus	6
Subacute bacterial endocarditis; bicuspid valves	2
Right subclavian artery distal to left subclavian artery (hemiplegia)	1
Right subclavian artery with long coarcted segment	1
Left subclavian artery involved in coarctation	1
Cerebral aneurysms	2
Proximal aneurysm	1
Long coarcted segment (2 inches)	1
Long coarcted segment; patent ductus arteriosus	1
Interventricular septal defect; patent ductus arteriosus	1
Absent transverse arch; patent ductus arteriosus	1
Total	18

instances the coarctation was of the infantile type and was associated with a patent ductus arteriosus; in two, the coarcted segment was deemed too long for removal. In one patient aneurysms were found both proximal and distal to the coarcted area; in another, an aneurysm was discovered distal to the coarctation. One patient showed evidence of aortic and pulmonary hypertension of undetermined origin.

Operation contraindicated: Three patients were denied operation by the clinician because of excessive atherosclerosis in the aorta. Their ages were 39, 41 and 42, respectively.

Deaths: Twenty-eight of the 118 patients included in this investigation died. Six died soon after birth; an additional eight were under three months of age at the time of death. Seven patients, all over 12 months of age, died before an operation could be performed.

Three patients died during surgery.[7] Four patients died postoperatively. An analysis of the findings at necropsy may be found in table 2.

TABLE 2.—*Deaths Occurring Among 118 Patients With Coarctation of the Aorta*

Classification	Findings	Incidence	No. of Cases
Newborn	All cyanotic with infantile type coarctation—plus ..		6
	Interventricular septal defect	1	
	Interatrial septal defect	1	
	Patent ductus arteriosus	3	
	Auriculoventricular communis	1	
Under three months	Adult type coarctation; endocardial sclerosis	1	8
	Infantile type coarctation; interventricular septal defect	2	
	Adult type coarctation; transposed vessels; aortic stenosis	1	
	Adult type coarctation; patent ductus arteriosus; interventricular septal defect	1	
	Adult type coarctation; patent ductus arteriosus; interatrial septal defect	1	
	Adult type coarctation; patent ductus arteriosus	1	
	Adult type coarctation; bicuspid aortic stenosed valves; patent ductus arteriosus	1	
Preoperative Deaths	(Patients over 12 months of age who died before operation could be performed—all with adult type coarctation) Additional pathology:		7
	Bicuspid aortic valves; stenosis	4	
	Cerebral aneurysm	1	
	Pneumonia	1	
	Bicuspid aortic valves; stenosis; mitral stenosis with failure (patient was 43 yrs. old)	1	
Deaths during Surgery	(All adult type coarctation) Additional pathology:		3
	Undiagnosed subaortic stenosis with standstill	1	
	Mitral stenosis; acute failure	1	
	Calcified bicuspid aortic stenosis; acute failure	1	

DISCUSSION

As a general rule, each patient demonstrating classic signs of coarctation of the aorta should undergo resection of the coarcted area. How-

TABLE 2.—*Deaths Occurring Among 118 Patients With Coarctation of the Aorta (Continued)*

Classification	Findings	Incidence	No. of Cases
Post-operative Death			4
	Thrombosis of aorta	1	
	Hemorrhage from site of anastomosis	1	
	Coronary sclerosis; infarction	1	
	Interventricular septal defect; failure	1	
Total deaths			28

ever, the presence of additional pathology may influence outcome of the operation. A defect commonly associated with coarctation is a patent ductus arteriosus which, in the presence of severe coarctation, is in effect a compensatory mechanism similar to the enlarged intercostal arteries that make up collateral circulation. A machinery murmur, especially if accompanied by a systolic thrill, audible in the second or third intercostal space beneath the clavicle and to the left of the cardiac border, will betray the presence of a patent ductus arteriosus. Confirmatory evidence includes elevation and dilation of the main and left pulmonary arteries.

A thrill over the aortic area accompanied by a loud murmur (suggestive of associated aortic stenosis) or a diastolic murmur at the apex of the heart (indicating mitral stenosis) may escape notice: surgery of the coarctation in the presence of either of these conditions usually has a fatal outcome. Diastolic murmurs over the base of the heart should suggest the presence of an associated insufficient bicuspid valve (aortic regurgitation).

If electrocardiographic tracings show right axis deviation, the coarctation is probably associated with lesions such as aneurysm of the pulmonary artery, patent ductus arteriosus, insufficiency of the pulmonary valve, or rheumatic valvular disease with atrial fibrillation. Serious conduction disturbances may contraindicate surgery. There is a case on record, for example, of complete heart block with Adams-Stokes syndrome, occurring in an adult with bicuspid calcareous aortic valves.[6]

Congenital aneurysm of the cerebral vessels is frequently associated with coarctation of the aorta; therefore, the head should always be auscultated carefully.

Bacterial endocarditis and aortitis are frequently found in association with congenital bicuspid arotic valves, a frequent complication of coarctation. If the coarctation has been severe, considerable vascular damage may have occurred; or, in the older patient, vascular changes incident to arteriosclerosis may contraindicate surgery.

CONCLUSION

Because the presence of associated abnormalities influences the outcome of surgical correction of the coarctation, intelligent presurgical planning must include the search for such defects. It has been the purpose of this paper to emphasize the frequent occurrence of such abnormalities, and to review those defects which most frequently accompany coarctation.

REFERENCES

[1] BROWN, G. E., JR., POLLACK, A. A., CLAGETT, O. T. AND WOOD, E. H.: Intra-arterial blood pressure in patients with coarctation of the aorta. Proc. Staff Meet., Mayo Clin. **23:** 129, 1948.

[2] BRUWER, A. AND PUGH, D. G.: A neglected roentgenologic sign of coarctation of the aorta. Proc. Staff Meet., Mayo Clin. **27:** 377, 1952.

[3] WELLS, B. G., RAPPAPORT, M. B. AND SPRAGUE, H. B.: The sounds and murmurs in coarctation of the aorta. Am. Heart J. **38:** 69, 1949.

[4] MASTER, A. M.: Right-sided aorta with atypical coarctation involving only the left subclavian artery, with hypertension. Am. Heart J. **32:** 778, 1946.

[5] BAHNSON, H. T., COOLEY, R. N. AND SLOAN, R. D.: Coarctation of the aorta at unusual sites. Am. Heart J. **38:** 905, 1949.

[6] CLARK, R. J. AND FIRMINGER, H. I.: Coarctation of the aorta associated with Adams-Stokes syndrome, complete heart block and bicuspid calcareous aortic valve. New England J. Med. **240:** 710, 1949.

[7] JACOBSON, G., COSBY, R. S., GRIFFITH, G. C. AND MEYER, B. W.: Valvular stenosis as a cause of death in surgically treated coarctation of the aorta. Am. Heart J. **45:** 889, 1953.

ABSTRACTS

BLOOD COAGULATION

Owen, C. A. and Cooper, T.: Parahemophilia. Arch. Int. Med. **95:** 194 (Feb.), 1955.

A father and his three children were found to have a defect in the mechanism for coagulation of blood known as parahemophilia or Owren's disease. This is characterized by a deficiency of the labile factor. Only in the father was the deficiency severe enough to cause bleeding. In agreement with published reports, both sexes in this family were involved and the inheritance was direct from one generation to the next, perhaps as the result of an incompletely dominant gene. Studies of 10 other relatives revealed no further instances of the disease.

The place of the labile factor and its closely related stable counterpart in the coagulation of blood is discussed. A deficiency of either factor is reflected in prolonged "prothrombin times" as determined by the Quick test, a situation unlike that in hemophilia, with its normal "prothrombin time." Treatment for the bleeding of parahemophilia consists of transfusions of fresh blood or plasma which, because of its freshness, is rich in labile factor.

BERNSTEIN

Horvath, S. M., Hamilton, L., Spurr, G., Allbaugh, E. and Hutt, B.: Plasma Expanders and Bleeding Times. J. Appl. Physiol. **7:** 614 (May), 1955.

Prolonged bleeding times have been reported as a complication in the use of dextran as a plasma expander. This difficulty may interfere with the clinical use of dextran. No decrease in prothrombin activity or the number of platelets has been found. This report attempts to evaluate the possibility that this hemostatic defect is caused by the presence of macromolecules in the circulation or the increase in plasma volume.

A constant amount of various plasma expanders was given each day for five consecutive days. Each morning before the infusion blood and plasma volumes were determined by means of I^{131} serum albumin and Wintrobe tube hematocrits. Bleeding times were measured in the ear and on the abdominal walls of rabbits and dogs. The various plasma expanders which are macromolecules did not consistently alter the hemostatic defect. These observations suggest that the presence in the circulation of macromolecules or the increase in plasma volume did not cause the hemostatic defect.

WECHSLER

Gubbay, E. R. and Pash, E.: Intramuscular Aqueous Heparin. Canad. M. A. J. **69:** 105 (Aug.), 1953.

Sixteen cases were treated with concentrated aqueous heparin, 6,250 international units injected intramuscularly every four hours. The method is simple and proved free of complications in our series. As judged by the effect on the clotting time good results were obtained in 10 cases and poor results in six cases. Four cases of myocardial infarction, clinically in a state of shock, had poor results.

These results do not suggest an increase of the intramuscular heparin dosage in serious cases of myocardial infarction. Such a procedure carries the risk of massive delayed absorption. In the absence of factors interfering with absorption, the routine use of concentrated aqueous intramuscular heparin at four-hour intervals may prove satisfactory.

BERNSTEIN

CONGENITAL ANOMALIES

Sodi-Pallares, D. and Marsico, F.: The Importance of Electrocardiographic Patterns in Congenital Heart Disease. Am. Heart J. **49:** 202 (Feb.), 1955.

Electrocardiographic criteria, used by the authors to recognize some of the congenital heart diseases, are discussed. The effects of atrial and ventricle septal defects on the atrial and ventricular complexes and on atrioventricular conduction are pointed out. The electrocardiographic alterations in patent ductus arteriosus, pure pulmonary stenosis, trilogy of Fallot, tetralogy of Fallot and Ebstein's Disease are considered.

RINZLER

Wood, P., Magidson, O. and Wilson, P. A. O.: Ventricular Septal Defect with a Note on Acyanotic Fallot's Tetralogy. Brit. Heart J. **16:** 387 Oct., 1954.

Ventricular septal defect occurred in 12.5 per cent of 750 cases of congenital heart disease. Of these, 8 per cent (60 cases) were isolated ventricular septal defects.

In analyzing the clinical characteristics of these 60 cases, the majority were found below the age of 15, although instances were seen in each decade up to the seventh. The sex ratio was equal.

Clinical manifestations are determined by the severity of the lesion. In severe lesions, growth is restricted and the pulse is small, in all but mild cases, a hyperdynamic left ventricular impulse is present. The second heart sound is usually split and a loud murmur and systolic thrill is almost always present. A functional mitral diastolic murmur is audible in 90 per cent of severe cases.

Radiology characteristically showed pulmonary plethora, dilatation of the pulmonary artery, a small aorta, enlargement of both ventricles and, at times, of the left atrium.

The electrocardiogram confirmed the physiologic situation. It was normal in mild cases but indicated enlargement of both ventricles, usually, if the lesion was severe, even in cases with right bundle branch block.

Differences in oxygen saturation between the pulmonary artery and right atrial samples averaged 7.5 in the mild, 13.5 in the moderate and 28 per cent in the severe cases. Pulmonary blood flow was also increased in the mild to 1.4, in the moderate to 2.3 and in the severe to 4 times the systemic flow. In eight severe cases with a high pulmonary vascular resistance, the pulmonary blood flow was only twice the systemic flow. Wood believes that a high pulmonary vascular resistance may be determined at birth.

Two instances of ventricular septal defect with aortic incompetence are described. Eleven instances of ventricular septal defect with pulmonary stenosis were present in 750 cases of congenital heart disease. The more important lesion is recognized clinically and the less obvious one by cardiac catheterization.

Ventricular septal defects of small degree are differentiated from: (1) mild pulmonary stenosis with normal aortic root which shows post-stenotic dilatation of the pulmonary artery, a widely split second sound and higher position of the murmur, (2) mild infundibular stenosis, (3) mild aortic and subaortic stenosis, (4) so-called innocent left parasternal murmur may all require cardiac catheterization for diagnosis and (5) acyanotic Fallot's tetralogy which shows right ventricular hypertrophy, a single second sound and is associated with effort intolerance.

Ventricular septal defects of large degree must be differentiated from: (1) mitral incompetence with anticlockwise rotation of the heart which shows P mitral, pure left ventricular dominance and enlargement of the left atrium, and (2) atrial septal defect which shows pure right atrial and ventricular enlargement. However in this lesion, as well as in patent ductus arteriosus, as the pulmonary vascular resistance rises, differentiation may be impossible without catheterization.

No individual died during this five-year period of observation. Subacute bacterial endocarditis was recognized only once. The incidence of ventricular septal defect was equally divided between mild, moderate and severe cases.

SOLOFF

Anderson, R. C.: Causative Factors Underlying Congenital Heart Malformations. Pediatrics **14:** 143 (Aug.), 1954.

A study was made of 205 cases of patent ductus arteriosus in which the diagnosis had been confirmed at surgery. Detailed family information was obtained in 117 cases, of which 105 were "uncomplicated" cases, four had a history of maternal Rubella, and eight had an additional cardiac defect but a negative history for maternal Rubella. In the "uncomplicated" group, there were 145 later-born siblings, two of whom had patent ductus arteriosus.

No cases of cousin marriage were reported in the parents of the 111 cases for whom this information was available. Patent ductus arteriosus occurred in five sets of twins, all discordant with respect to the defect, and including two definitely uniovular pairs, two probably uniovular pairs, and one probably binovular pair. No evidence was found of a birth order effect for patent ductus arteriosus cases, but a definite seasonal incidence was noted for cases associated with maternal Rubella or having additional cardiac defects.

It was concluded that there is a definite familial tendency to the occurrence of patent ductus arteriosus. The risk figure for the recurrence of congenital heart defects in later-born siblings is of

the order of one in 50. It was suggested that patent ductus arteriosus is not an entity of single etiology, but that it depends on various prenatal as well as possible natal factors.

BERNSTEIN

Shephard, R. J.: Pulmonary Arterial Pressure in Acyanotic Congenital Heart Disease. Brit. Heart J. **16:** 361 (Oct.), 1954.

The pressure/flow relationships of 24 instances of patent ductus arteriosus are compared to those of 17 with atrial septal defects and 14 with ventricular septal defects.

The pulmonary artery systolic pressure is normal or just above normal in those with patent ductus, high in those with atrial septal defects and approaches the left ventricular pressure in those with ventricular septal defects. Diastolic pressure is increased in all, with the pulse pressure widened in the last two. A small pressure gradient across the pulmonary valve is present in all three, but the pressure change is gradual.

Hypertension cannot be explained by the estimated size of the shunt or pulmonary blood flow. Hypertension is determined by the ventricular septal defect. In atrial septal defect, age may be the determining factor.

Pulmonary artery resistance also appears to increase with age and is associated with arterial unsaturation.

SOLOFF

CORONARY ARTERY DISEASE

Lyons, B. H. and Lyons, R.: Coronary Artery Disease in Pregnancy. Canad. M. A. J. **71:** 267 (Sept.), 1954.

Coronary disease in pregnancy is a rare event. Fourteen acceptable cases have been found in the literature and a further case is reported of a patient with coronary disease who successfully carried through a pregnancy.

Of the 15 reported patients, 13 survived. The two patients who developed infarction in the third trimester died. It is suggested that it is at this period that infarction is likely to be fatal.

While available information on which to base opinions is scanty, it is suggested that pregnancy be avoided in the presence of coronary disease. If the patient is already pregnant and there are no other contraindications, it may be justifiable to try to carry the patient along with great care and vigilance.

BERNSTEIN

BACTERIAL ENDOCARDITIS

Antel, J. J., Rome, H. P., Geraci, J. E. and Sayre, G. P.: Toxic-Organic Psychosis as a Presenting Feature in Bacterial Endocarditis. Proc. Staff Meet., Mayo Clinic **30:** 45 (Feb.), 1955.

The condition of a patient with subacute bacterial endocarditis is described. A toxic-organic psychosis (acute brain syndrome) was the initial presenting feature. Necropsy disclosed syphilitic aortitis and aortic valvular bacterial endocarditis. The content of the psychologic reaction is described and a sketch of the relevant premorbid personality outlined. The relationship between these is discussed briefly in terms of an attempt by an organism to maintain psychologic homeostasis in the face of stress.

SIMON

Roantree, R. J. and Rantz, L. A.: Fatal Staphylococcal Endocarditis Treated with Erythromycin Arch. Int. Med. **95:** 320 (Feb.), 1955.

Because the *staphylococcus* has the ability to develop resistance when exposed to currently used antibiotics, the treatment of staphylococcal disease and particularly of endocarditis, is most difficult. The reported case well illustrates the emergence of a strain resistant to erythromycin. In vitro studies help to clarify the problem and show that resistant variants may appear from the great majority of staphylococcal strains.

The case described here is of interest from several other viewpoints. The causative organism was a coagulase-negative *staphylococcus albus*. Infection was discovered following mitral valvotomy, a fairly rare occurrence, despite the theoretic probability of such an event. The immediate cause of death seemed to be the occlusion of the mitral orifice by a large vegetation.

BERNSTEIN

CONGESTIVE HEART FAILURE

Greiner, T., Gold, H., Palumbo, F., Warshaw, L., McGowan, T., Weaver, J. and Otto, H.: Bioassay of the Diuretic Potency of Xanthines and the Organic Mercurials in Patients With Congestive Failure. J. Pharmacol. & Exper. Therap. **113:** 140 (Feb.), 1955.

Xanthine materials are more often included as diuretic agents than any other substance. However, their place in relation to other agents is unknown. This paper presents a method for bioassay of diuretic agents in ambulant patients with congestive failure. The method was applied in order to compare the potency of aminophylline with Mercuhydrin, to determine the degree to which the diuretic action of Mercuhydrin may be increased by aminophylline, to compare the diuretic action of aminophylline by intramuscular and oral administration and to compare the therapeutic value of oral theophylline in the form of ethylenediamine with that of the calcium salt.

The subjects are ambulant adults (39 to 79 years) with congestive failure due to all types of heart disease. Their salt intake is moderately restricted. The diuretic effect is measured by the body weight loss 24 hours after the dose. Mercuhydrin is used as the standard and this drug, plus the test material, is given at random at each clinic. The results supply

data for dosage response curves, which are checked by conventional statistical methods.

In terms of mM, intramuscular Mercuhydrin is about 10 times as potent as intramuscular aminophylline. One-half Gm. of aminophylline and only 0.6 ml. of Mercuhydrin produced the same diuretic effect. Therefore, the usual 2 cc. dose of Mercuhydrin is more effective than the usual 0.5 Gm. dose of aminophylline. Oral aminophylline (0.4 Gm.) is less effective than the intramuscular aminophylline, producing an equivalent diuretic response to 0.4 ml. of Mercuhydrin intramuscularly. Larger oral doses of aminophylline (0.8 Gm.) produced disturbing gastrointestinal symptoms in 70 per cent of patients. Oral calcium theophyllinate and aminophylline give the same diuretic response on the basis of millimols or weight. However, oral aminophylline produces fewer gastrointestinal symptoms. Intramuscular aminophylline enhanced the diuretic effect of Mercuhydrin by 50 per cent. This effect is additive or less and is less than that due to ammonium chloride, which causes an effect with Mercuhydrin in excess of simple summation.

It is their experience that aminophylline may enhance a subeffective diuretic regime but the intensification of the regime with the mercurial diuretic alone accomplishes the same result. There is no proof for the assumption that the xanthines will restore diuretic response in patients refractory to the organic materials.

WECHSLER

Rubin, A. L., Thompson, H. G., Jr., Braveman, W. S. and Luckey, E. H.: The Management of Refractory Edema in Heart Failure. Ann. Int. Med. **42:** 358 (Feb.), 1955.

In this study, in nine episodes of refractory edema due to congestive heart failure, restoration of responsiveness to mercurial diuretics was accomplished by the production of a hyperchloremic acidosis. Diamox, or a combination of Diamox and ammonium chloride, was used to produce this hyperchloremic acidosis. No untoward effects of either the hyperchloremia or acidosis were observed in this study. In the patients who are unresponsive to mercurial diuretics, Diamox is ineffective as a diuretic agent. However, a moderate hyperchloremic acidosis is produced by Diamox irrespective of diuretic response. When Diamox and Mercuhydrin are administered on the same day, optimal diuretic response does not occur. Maximal diuresis with Mercuhydrin occurred the second day after Diamox was discontinued.

WENDKOS

Barger, A. C., Ross, R. S. and Price, H. L.: Reduced Sodium Excretion in Dogs With Mild Valvular Lesions of the Heart, and in Dogs With Congestive Failure. Am. J. Physiol. **180:** 249 (Feb.), 1955.

Right sided congestive failure was produced by combined tricuspid insufficiency and pulmonary stenosis. In these animals there was a marked reduction in sodium excretion but the ability to excrete water was only moderately lower than control values. If atrial pressure was elevated 10 to 14 cm. H_2O by tricuspid insufficiency, a moderate reduction in sodium excretion was observed with normal water excretion. However, pulmonary insufficiency which failed to elevate right atrial pressure produced a small but statistically significant decrease in sodium excretion. On the other hand, reduction of the diameter of the pulmonary artery by one half which elevated right atrial pressure 2 to 4 cm. H_2O produced no change in sodium excretion. In normal dogs, exercise increases the eight hour sodium excretion. However, this is not true in animals with tricuspid insufficiency. It is emphasized that changes in the peak sodium excretion may take place earlier than usually suspected.

OPPENHEIMER

White, T. J., Leevy, C. M., Brusca, A. M. and Gnassi, A. M.: The Liver in Congestive Heart Failure. Am. Heart J. **49:** 250 (Feb.), 1955.

Biochemical liver function tests and needle biopsies of the liver were performed on 75 patients with congestive heart failure and correlated with clinical features. A composite of clinical, biochemical, and histologic study was helpful in patients with hepatomegaly or fluid accumulation resistant to treatment. Serial biopsy studies demonstrated two mechanisms leading to liver fibrosis in heart failure: (a) passive congestion led to central necrosis and centrilobular fibrosis and (b) poor nutrition caused fatty liver and eventually diffuse fibrosis. Survival periods were related to the severity of hepatic changes in patients with fibrosis or necrosis and to the type of heart disease and the degree of heart failure in the others. Icterus, hypoalbuminemia and diffuse fibrosis were often accompanied by fluid retention refractory to therapy. The prognosis in these cases was poor.

RINZLER

Dubilier, W., Taylor, T. L. and Steinberg, L.: Aortic Sinus Aneurysm Associated with Coarctation of the Aorta. Am. J. Roentgenol. **73:** 10 (Jan.), 1955.

In a series of 58 angiocardiographic studies for coarctation of the aorta, three cases of localized aneurysmal dilatation of the aortic sinus were discovered. All had hypertension in the upper extremities (in the one with a blood pressure of 196/13 no clinical data for aortic regurgitation was offered).

The possibility of rupture of the aorta at this site is discussed, since it is said to occur as a cause of death in 22 per cent of patients with coarctation, exceeding the 12 per cent dying of cerebral hemor-

rhage, and second only to the 30 per cent dying of heart failure.

SCHWEDEL

Sigler, L. H.: The Role of Hypertension in the Etiology and Prognosis of Coronary Occlusion. Ann. Int. Med. **42:** 369 (Feb.), 1955.

An analysis was made of 1160 cases of coronary occlusion to determine whether hypertension affects the incidence and prognosis of the disease. The series consisted of 946 males and 214 females. Of these, 797 were still alive and 363 were dead at the time this report was compiled. Each patient had had many blood pressure determinations over the years of observation, both before and after the onset of coronary occlusion. The cases were divided into four blood pressure groups, as follows: group I, systolic up to 140, diastolic up to 90; group II, systolic 141 to 160, diastolic 91 to 100; group III, systolic 161 to 200, diastolic 101 to 110 and group IV, systolic above 200, diastolic above 110. In the last group there were some cases with blood pressures as high as 300 systolic and 170 diastolic. Each blood pressure group was subdivided: (1) by the decade of life in males and females when the first attack of coronary occlusion occurred; (2) the average longevity following the first attack of coronary occlusion and (3) the length of survival of more than one, five, and 10 years, following the first attack of coronary occlusion. The ratio of males to females who had coronary occlusion was 4.4:1, whereas hypertension was about twice as frequent in females as in males. In males, coronary occlusion begins to appear earlier in life and its incidence progressively rises, reaching a fastigium between 50 and 59 years. The same is true of females but here the fastigium is reached between 60 and 69 years. The incidence of hypertension likewise increases with age, but such an increase does not correspond strictly to the increase in coronary occlusion. Relatively more males than females in the over-all age groups who had the first attack of coronary occlusion belonged to the lower blood pressure groups. Up to 50 years of age, however, even females had a relative predominance of cases in the lower blood pressure groups. Of the 363 patients who died, the few who died before 40 years of age were all in the normotensive group, except for one who died from uremia who was markedly hypertensive. After that age, there was a progressive increase in deaths following coronary occlusion with advancing age, but such increase did not correspond to the increase in blood pressure. A greater percentage of males than females lived more than one, five and 10 years following occlusion. However, a greater percentage of hypertensive than normotensive females survived these periods. The figures do not appear to indicate that hypertension has any definite causal and prognostic relationship to coronary occlusion. The discrepancies in the figures are considered to be due to differences in the number of male and female patients in this series who had coronary occlusion and to the relatively greater percentage of female hypertensives.

WENDKOS

Katz, A. M., Katz, L. N. and Williams, F. L.: Regulation of Coronary Flow. Am. J. Physiol. **180:** 392 (Feb.), 1955.

Effective perfusion pressure is defined as aortic minus coronary venous pressure. This entity is directly related to coronary flow. Cardiac output does not directly determine coronary flow, since the flow may be unchanged if aortic pressure is held constant while output increases. Nevertheless, at blood pressures near the upper limit of normal, increasing the output does increase coronary flow even though pressure is maintained constant. Oxygen use of the heart and coronary vascular resistance were not closely related. Where correlations existed, they were best between coronary venous oxygen content and coronary resistance. Many factors affecting coronary flow do not act directly. Their action is complex.

OPPENHEIMER

Michaelides, G. and Papadopoulos, A.: The Prognosis of Ischemic Necrosis of the Myocardium. Arch. mal. coeur **48:** 190 (Feb.), 1955.

Five hundred cases of recent myocardial infarction were followed up over a period of five years. In 400 treated without anticoagulants, the immediate mortality (within the first four weeks) was 14 per cent. In 100 cases submitted to treatment with anticoagulants, there was no instance of thromboembolism and the mortality was 8.5 per cent. The evaluation of longterm prognosis was based on the capacity of the patient to resume his work and to lead a normal life. Three groups could be distinguished: 37 per cent of the material showed full recovery and 70 per cent of these patients were alive after seven years. Fifty per cent recovered to limited working capacity. The remaining 13 per cent were unable to resume work and none of this group survived longer than two years.

PICK

Nesvadba, P.: Cardiac Rupture following Myocardial Infarction. Cardiologia **26:** 103 (Fasc.2), 1955.

Following a review of the literature, the author reports on 44 of his own observations on cardiac ruptures subsequent to myocardial infarction. Among 5,235 autopsies performed in a large general hospital over a period of five years, recent myocardial infarction constituted the cause of death in seven per cent, in 12 per cent of the latter it was associated with cardiac rupture. In 66 per cent of the material, this took place on the third or fourth day after coronary occlusion. In 64 per cent, the rupture occurred in the supra-apical region of the anterior

wall, in seven per cent in the right ventricle but only in infarcts involving the ventricular septum. The longest survival time in the present series was two days. In half of the cases terminated by cardiac rupture, the blood pressure was elevated. Other factors involved in this complication appear to be physical activity, the use of anticoagulants and the condition of the myocardium at the time of the coronary occlusion, in particular, recurrent myocardial infarction. The clinical signs of developed rupture are described. An electrocardiographic sign, which may herald impending rupture, is persistent or recurrent ST-T alterations characteristic for the recent stage of infarction.

PICK

Jacobson, E.: Principles Underlying Coronary Heart Disease. Considerations for a Working Hypothesis. Cardiologia **26:** 83 (Fasc.2), 1955.

Patients with angina pectoris and coronary heart disease are usually tense personalities with overactivity of their adaptive behavior. The somatic consequences of such a condition can be determined by recording action potentials of skeletal muscles and on the basis of spastic contraction in various portions of the gastrointestinal tract at X-ray examination. Such excessive neuromuscular activity and hyperkinesis leads to arteriolar constriction and cardiac work and is often manifested in form of arterial hypertension.

The author believes that coronary heart disease, as a rule, results from habitual overdrive of the human organism with or without concomitant emotion. Early stages would be marked by vasoconstriction with cardiac hypoxia and angina pectoris, accompanied in most instances with alimentary spasticity and, in about half the cases, by incipient hypertension. With continued wear and tear in many aging individuals, particularly males, coronary heart disease develops from a stage of insufficient distensibility of the vessels to dystrophy of the arterial wall and thickening of the intima. Unless requirements are reduced for coronary blood supply, hemorrhage may occur into the sclerotic intima of the vessels or a thrombus may form. Thus, upon undiminished drive of the organism, final stages are reached marked by arterial occlusion and/or anoxia of the myocardium leading to infarction with heart failure, in part or in total. It would appear on this basis, that relaxation of the skeletal muscles is an important prophylactic and therapeutic factor in coronary disease. The recording and measurement of action potentials of extremity muscles may be valuable in this regard.

PICK

Keys, A.: Obesity and Degenerative Heart Disease. Am. J. Pub. Health **44:** 864 (July), 1954.

Overweight per se, except when it is of extreme degree, is not a primary cause of coronary disease and the myocardial disorder to which it gives rise. There is some evidence, however, that excess weight may contribute to the development of hypertensive heart disease. Dieting to lose weight is highly desirable in true obesity, but a mere reduction in general food consumption is not likely to accomplish reduction of our heart disease mortality to the level prevailing in countries with the most favorable records in this regard.

Large-scale, long-range studies bringing physiologic principles to bear in research on population samples are essential if preventive measures against heart disease and other metabolic ailments are to be discovered and brought into application. Campaigns against overweight are of benefit but cannot be a substitute for research or for a knowledge of physiologic hygiene which we do not yet have.

BERNSTEIN

Chieffo, H. and Casciano, A. D.: Combined Anterior and Posterior Myocardial Infarction. Arch. Int. Med. **95:** 834 (June), 1955.

An electrocardiographic study of three interesting cases of combined anterior and posterior myocardial infarction is presented. The well-known tendency toward neutralization or dominance of the electric effects of a recent infarct over those of an old infarct is demonstrated. It is also shown that this neutralization effect is often incomplete and that the diagnosis of a double infarction in opposite walls can be suspected in many instances by careful analysis of even a single electrocardiogram. Serial tracings naturally increase diagnostic accuracy in such problems. An interesting pattern of double acute infarction involving both the anterior and posterior surfaces of the heart is also discussed. A review of the literature shows that an acute or recent anteroposterior infarction is fairly common and has an incidence of approximately 10 per cent. A new concept is offered to explain the occurrence of such a lesion either as a single, large confluent infarct or as two distinct lesions.

BERNSTEIN

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, AND BALLISTOCARDIOGRAPHY

Pescador, L., Martin de Prades, B. and Sainz, V.: Alternating Ballistic Pulse. Cardiologia **26:** 121 (Fasc. 2), 1955.

Thirteen cases are presented with alternation in the ballistocardiogram recorded in patients with a variety of cardiovascular diseases. In most, the alternation involved the J wave, in one only, the H wave. In three cases alternation in the size of all components occurred in consecutive groups of three beats. In no instance was ballistocardiographic alternation associated with a pulsus alternans in the systemic circulation. On the other hand, three cases with pulsus alternans showed no alternation in the

ballistocardiogram. It must be assumed that on this basis the ballistocardiographic phenomenon is a reflection of alternation in the pulmonary circulation and may be the only test to demonstrate right ventricular failure. The authors consider a B_1 deficiency as a primary etiologic factor in these cases.

PICK

Siecke, R.: The Influence of the P-R Interval upon the Amplitude of the First Heart Sound, particularly in Complete A-V Block. Ztschr. Kreislaufforsch. **44:** 109 (Feb.), 1955.

The authors studied the relation of the amplitude of the first heart sound to the length of the respective P-R interval in phonocardiograms of 10 patients with complete A-V dissociation and in three cases with A-V nodal escapes. With a very short P-R, to about 0.05 second, the oscillations of the first sound are small, to become large when P-R duration approaches 0.10 second. Beyond this value there is a very marked drop in amplitude. It remains constant up to 0.20 second, but further decreases to minimal values up to a P-R of about 0.70 second. With P-R longer than that, there is another increment of oscillations comparable to those at the very short P-R. Absolute measurements of the amplitude of the oscillations revealed great variations apparently dependent on the age of the patient, being larger in children than in older people. With equal P-R intervals, the duration of the preceding diastole has no influence on the loudness of the first heart sound.

The variations in the intensity of the first heart sound are dependent on both, the dynamics of the ventricles and the position of the A-V valves at the onset of ventricular contraction. Although the latter factor is important, alterations in the temporal sequence of the various phases of ventricular contraction must also be taken into consideration. The diagnostic significance of a loud or muffled first heart sound in estimating the A-V conduction time at the bedside is discussed.

PICK

Friese, G.: Clinical Observations Concerning Reduction of Voltage in the Electrocardiogram during Dilatation of the Heart. Arch. Kreislaufforsch. **44:** 99 (Feb.), 1955.

Electrocardiograms are shown of five selected cases with congestive heart failure of different etiology, exemplifying decrease of voltage in limb and precordial leads at the time of heart failure and return to original amplitude following compensation. Correlation with the size of the heart shadow at the different stages revealed an inverse relationship. An enlargement of the heart size was associated with reduction of the amplitude in the electrocardiogram and vice versa. The authors ascribe the alterations of the size of the cardiac silhouette to varying grades of dilatation of the heart chambers and the alterations in the manifest potential differences to associated short circuits, effected in the electric field by the increase of intracardiac blood volume.

PICK

Marsico, F., Penaloza, D., Tranchesi, J., Limon, R., and Sodi-Pallares, D.: The Electrocardiogram in Ventricular Septal Defect: Scalar and Vectorial Analysis of Thirty-Two Cases. Am. Heart J. **49:** 188 (Feb.), 1955.

Thirty-two cases with ventricular septal defect, diagnosed by cardiac catheterization, were studied. In all cases the 12 usual leads were recorded by a Sanborn photographic apparatus. In an effort to investigate the course of the ventricular activation process, a special study was made with multiple and simultaneous thoracic leads in six cases, using the Sanborn Polyviso four-channel electrocardiograph for direct simultaneous recording. The electrocardiograms were studied from the scalar and vectorial viewpoints.

In summary, the electrocardiographic signs of ventricular septal defect are: (1) Right ventricular hypertrophy with systolic overloading of the right ventricle: (a) tall R wave in V_1 and V_2; (b) QRS complex of the rR, Rs, R, and qR type. (2) Left ventricular hypertrophy with or without diastolic overloading of the left ventricle in V_5 and V_6: (a) tall or normal R wave when a small deflection was expected due to the accentuated right ventricular hypertrophy; (b) deep Q wave; (c) delayed intrinsicoid deflection; (d) positive T wave; (e) frequent complexes of QRS type with a positive T wave. (3) Suggestive data of septal hypertrophy: deep Q wave in V_5 and V_6 which is inscribed simultaneously with the first positivity of a complex of the rR type in V_1. (4) Large diphasic complexes in V_2, V_3 V_4 and on occasion in the limb leads.

RINZLER

Schrire, V. and Vogelpoel, L.: The Clinical and Electrocardiographic Differentiation of Supraventricular and Ventricular Tachycardias with Regular Rhythm. Am. Heart J. **49:** 162 (Feb.), 1955.

A clinical and electrocardiographic evaluation of 79 cases of paroxysmal tachycardia with regular rhythm was made.

Internal jugular venous pulsations were carefully inspected while palpating the opposite common carotid artery. Though it was usually impossible to identify the individual venous waves at these rapid rates, gross dissociation between atrial and ventricular rates could usually be detected. Special effort was made to identify the presence or absence of "Cannon A" waves and when present, their regularity or irregularity was noted. During auscultation, attention was concentrated on the first and second heart sounds at the mitral area, the fourth left space at the sternal edge and the pulmonary area. The presence or absence of any variation in the intensity

of the first heart sound during held respiration was noted. Particular care was paid to the presence or absence of splitting of the heart sounds and to the degree of splitting when present. Splitting of the first heart sound was best heard at the fourth left space and of the second heart sound at the pulmonary area. The Sanborn-Stethocardiette was used to obtain phonocardiograms in each case. Logarithmic (high frequency) sound tracings, which give an accurate graphic representation of human hearing, were recorded synchronously with a suitable electrocardiographic lead, carotid or jugular pulse tracing. The sound recordings were taken in succession from the mitral area, fourth left space and pulmonary artery. Tracings were usually recorded at normal electrocardiographic speed (25 mm. per second), but to permit more accurate study, recordings were always made at fast paper speed (75 mm. per second). The carotid and jugular tracings were obtained by placing a crystal microphone directly on the neck, thus avoiding delay from air conduction.

In a case of rapid regular tachycardia, if the first and second sounds are single or normally split, the diagnosis of supraventricular tachycardia can be made with confidence and ventricular tachycardia can be excluded with confidence. In a case of rapid regular tachycardia, if there is wide splitting of both sounds, ventricular tachycardia is usually present. In a case of rapid regular tachycardia, if there is wide splitting of both sounds, variation in the intensity of the first sound and independent, irregular "Cannon A" waves in the jugular venous pulse, the diagnosis of ventricular tachycardia can usually be made with confidence. Supraventricular tachycardia with bundle branch block, ventricular tachycardia with atrial fibrillation and ventricular tachycardia with retrograde conduction are all rare conditions in which ventricular asynchrony occurs without atrioventricular dissociation. Wide splitting of both heart sounds, without variation in the intensity of the first sound, is therefore encountered. Differentiation is difficult, but can be made by careful study. In the case of rapid regular tachycardia, if the electrocardiogram reveals a QRS interval of normal duration, the diagnosis of supraventricular tachycardia is established. Atrial activity can usually be demonstrated by standard electrocardiograms and esophageal leads are rarely necessary. In a case of rapid regular tachycardia, if the electrocardiogram reveals a widened QRS, supraventricular tachycardia with bundle branch block cannot be differentiated from ventricular tachycardia, unless atrial activity is demonstrated. Whereas clinical evidence of atrial activity can be readily detected, the diagnosis cannot usually be made by the conventional electrocardiogram, as the P waves are often obscured by the widened QRS-T complexes. The esophageal leads, however, will clearly demonstrate P waves and thus overcome this problem. The esophageal lead is essential in the differentiation of supraventricular tachycardia with bundle branch block, ventricular tachycardia with independent atrial activity, ventricular tachycardia with retrograde conduction and ventricular tachycardia with atrial fibrillation.

RINZLER

Scherf, D., Blumenfeld, S., Golbey, M., Ladopoulos, C. and Roth, F.: Experimental Studies on Arrhythmias Caused by Focal Cooling of the Heart. Am. Heart J. **49:** 218 (Feb.), 1955.

Investigations were performed on dogs and cats to study the effect of cooling on fibrillation of the atria and to determine the influence of the ventricular rate on the appearance of ventricular fibrillation. In addition, the effect of preventive measures such as pretreatment with atropine or quinidine was explored.

Focal cooling of the right atrium over a period of 20 minutes during sinus rhythm caused atrial fibrillation only once in 10 experiments. Cooling of the right atrium during atrial fibrillation caused by topical application of aconitine on the left atrium stopped the fibrillation five times in nine experiments. Cessation of the cooling led to the immediate reappearance of the fibrillation. Focal cooling of the ventricle frequently caused A-V block and intraventricular block in the cat, but rarely caused these effects in the dog. The appearance of A-V block during focal cooling of the ventricles prevented high ventricular rates and therefore prevented the development of ventricular fibrillation. Focal cooling provoked ventricular but not atrial extrasystoles. Not infrequently, extrasystoles could be elicited by cooling the right ventricle but not by cooling the left. Extrasystoles in groups, multiple extrasystoles and ventricular tachycardias were more common in the atropinized dog; this was due to the delay in onset of ventricular fibrillation following the use of this drug. Ventricular fibrillation appeared in one experiment three seconds after discontinuation of the cooling. The experiments clearly showed that ventricular fibrillation appeared more readily with higher rates. Its appearance was delayed or prevented after administration of atropine and particularly quinidine, but with ventricular rates of 300 and above, focal cooling always elicited it. After atropine and quinidine the duration of the prefibrillatory state was prolonged.

RINZLER

ENDOCRINE EFFECTS ON CIRCULATION

Frank, H. A., Jacob, S., Weizel, H. A. E., Reiner, L., Cohen, R. and Fine, J.: Effects of ACTH and Cortisone in Experimental Hemorrhagic Shock. Am. J. Physiol. **180:** 282 (Feb.), 1955.

Irreversible hemorrhagic shock was produced in dogs. In this experimental situation, cortisone or corticotropin (ACTH) did not improve blood flow or

increase survival time. Although there was a brief increase in blood pressure after ACTH, this is probably due to its Pitressin content. Adrenal cortical total lipoid or carbonyl-containing lipoid was not depleted in the agonal period of irreversible shock. Under these circumstances, changes in cholesterol lipoid were inconstant. ACTH during shock did not increase adrenal cortical lipoid depletion. However, both cortisone and ACTH did increase histologic damage in the adrenal cortices of dogs who were in a state of irreversible hemorrhagic shock.

OPPENHEIMER

Nickel, J. F., Smythe, C. McC., Papper, E. M., and Bradley, S. E.: A Study of the Mode of Action of the Adrenal Medullary Hormones on Sodium, Potassium and Water Excretion in Man. J. Clin. Invest. **33:** 1687 (Dec.), 1954.

The mechanism of the renal function response to *l*-epinephrine and *l*-norepinephrine in man was studied by renal clearance technics. During the pressor action of these infused adrenal medullary hormones, there is a decrease in sodium and potassium excretion, as well as a tendency to lose water in the urine. These changes are not mediated through the adrenal cortex because they were found in three patients with either Addison's disease or bilateral adrenalectomy. The output of dilute urine can be explained by diminished formation of antidiuretic hormone. Studies with Pitressin indicate an independence of changes in electrolytes and water reabsorption by the renal tubules.

The response does not seem to be mediated through neural pathways because high spinal anesthesia did not block the activity of the hormones. Furthermore, the pressor action was not essential because *l*-epinephrine produced the typical renal changes in doses too small to evoke a pressor response, and other pressor agents (e.g. angiotonin, ephedrine) did not show similar electrolytic changes.

The data suggest that a reduction of blood flow to the tubules affects sodium reabsorptive activity, and that intrarenal vasoconstriction appears to affect potassium retention.

WAIFE

Sturtevant, F. M. and Hassen, N.: Increased Sensitivity to Salt in Rats Pretreated with Desoxycorticosterone. Am. J. M. Sc. **229:** 188 (Feb.), 1955.

Rats, receiving desoxycorticosterone acetate (DCA) and saline, developed hypertension within a few days. Upon withdrawal of the hormone and saline drinking fluid, normotension was restored promptly. However, readministration of the isotonic saline resulted in the reappearance of hypertension in the DCA-treated animals. It is suggested that experimental hypertension induced by DCA is an accelerated form of the disease produced by high salt intake alone. The elevation of blood pressure is a consequence of some more fundamental disturbance in the regulation of electrolyte distribution and excretion.

SHUMAN

Heidorn, G. H., Schemm, F. R., and Layne, J. A.: The Varied Patterns of Water and Sodium Diuresis during Corticotropin (ACTH) Therapy of the Nephrotic Syndrome. Am. J. M. Sc. **229:** 18[illegible] (Feb.), 1955.

Seven patients with nephrotic syndrome were treated with corticotropin (ACTH) during which balance studies for sodium and potassium were performed. Estimated weight changes were calculated from sodium balances and compared to actual weight in order to estimate the proportionate water to salt diuresis or retention for a given period. Varied patterns of water and sodium balances were observed in these patients. The loss of edema fluid was greatest, usually beginning 24 hours after ACTH was stopped. In most instances, sodium was lost in excess of water. However, proportionate loss of water and sodium or an excess of water over sodium loss was also observed in the post-ACTH period. Weight gain, when observed during the course of treatment, was due more to water retention than to sodium retention. The responsiveness of nephrotic or cardiac patients to mercurial diuretics can be regained after or during a course of ACTH administration. The qualitative response of the tubules to mercurial diuretics is altered by ACTH in that a water diuresis occurred early in the treatment period, while a salt diuresis in excess of water occurred later in the course of hormonal therapy.

SHUMAN

Hawthorne, E. W., Brownlee, G. V., and Pogue, W. G.: Arterial Pressure Changes in Experimental Renal Hypertensive Dogs Following Production of Femoral Arteriovenous Fistula. Am. J. Physiol. **180:** 65 (Jan.), 1955.

Renal hypertension was produced in dogs by either mild constriction of the left renal artery or by controlled constriction of the abdominal aorta. If a femoral arteriovenous fistula is produced in one of these animals, blood pressure returns to control levels. At this time there is no increase in pulse pressure. The suggestion is made that an increase in intrarenal volume pulsations may account for the hypotensive effect of the fistula.

OPPENHEIMER

Friedman, S. M., Nakashima, M. and Friedman, C. L.: Specificity of Depressor Effect of Pitressin. Am. J. Physiol. **180:** 57 (Jan.), 1955.

In rats made hypertensive with desoxycorticosterone acetate, a delayed depressor response to subcutaneous Pitressin begins about five hours after administration. A single large dose will also

elicit this response. Pitocin has no such action. Pituitrin in daily doses produces an observed depression in the base line of blood pressure, although no depressor response is detected. The depressor action is specific for Pitressin.

OPPENHEIMER

Sturkie, P. D. and Ringer, R. K.: Effects of Suppression of Pituitary Gonadotrophins on Blood Pressure in the Fowl. Am. J. Physiol. **180:** 53 (Jan.), 1955.

In chickens, blood pressure of the adult male is 20 per cent higher than that of females. However, the castrated male has a pressure which is the same as normal males. The sexual development and output of pituitary gonadatrophins is depressed by diethylstilbesterol and 2-amino, 5-nitrothiazole in normal and castrated males as well as in females. These materials depress blood pressure in normal males and capons but not in females. Pregnant mare serum increased blood pressure in normal and castrate males (pressure previously depressed with diethylstilbesterol) but was without any effect on blood pressure in females. The authors suggest that differences in pituitary gonadotrophin utilization account for the spread in the level of blood pressure of normal males and females rather than differences in production of them.

OPPENHEIMER

Goodyer, A. V. N. and Jaeger, C. A.: Renal Response to Non-Shocking Hemorrhage-R le of the Autonomic Nervous System and of the Renal Circulation. Am. J. Physiol. **180:** 69 (Jan.), 1955.

Water as well as sodium and chloride excretion was reduced by limited, nonshocking hemorrhage. These changes were not prevented by hexamethonium or unilateral renal denervation. Blood pressure did not fall. Mean changes of filtered sodium and those of renal plasma flow were not significant. If shed blood was retransfused, renal excretory functions were returned to control values. This is true, despite autonomic blockade, renal denervation, constant arterial blood pressure and insignificant changes in filtered sodium and renal plasma flow.

OPPENHEIMER

Salgoado, E. and Selye, H.: Hormonal Factors in the Production of Experimental Renal and Cardiovascular Disease. J. Lab. & Clin. Med. **45:** 237 (Feb.), 1955.

Previous studies demonstrated that the administration of large doses of methylandrostenediol (MAD) to rats produced a syndrome consisting of nephrosclerosis, myocarditis, periarteritis nodosa, hypertension and polyuria, very similar to the one produced by mineralocorticoids such as desoxycorticosterone acetate (DCA). This effect of methylandrostenediol is presumably mediated through the adrenals, since previous experiments have shown that it cannot be obtained after adrenalectomy.

The present experiments show that procedures which enhance the cardiovascular toxicity of mineralo-corticoids, such as unilateral nephrectomy and a high sodium intake or simultaneous treatment with somatotrophic hormone (STH), also enhance the corresponding toxic effects of methylandrostenediol. These same procedures also augment the ability of methylandrostenediol to induce the accumulation within the adrenocortical cells of periodic acid-Schiff positive granules. None of these procedures exert a significant effect upon such a rather typical sexual action of methylandrostenediol as the stimulation of the preputial glands.

CORTELL

Conn, J. W.: Primary Aldosteronism. J. Lab. & Clin. Med. **45:** 661 (April), 1955.

The author had previously described a new clinical syndrome designated as primary aldosteronism and characterized by the presence in the urine of excessive amounts of a sodium-retaining corticoid (aldosterone), by severe hypokalemia, hypernatremia, alkalosis and a renal tubular defect in the reabsorption of water. The clinical picture consisted of intermittent tetany, paresthesias, periodic severe muscular weakness and "paralyses," polyuria and polydipsia, hypertension and no edema. There was a *relative* lack of important symptomatology at extremely low levels of serum potassium, and no other demonstrable evidence of increased activity of the adrenal cortices. (Conn, J. W.: J. Lab. & Clin. Med. **45:** 6 (Jan.), 1955.)

The present report gives the postoperative results in a patient with the above syndrome in whom an adrenal tumor was removed from the right side along with the right adrenal gland. Postoperatively, the patient showed a reversal of all the chemical deviations which characterized the syndrome. There was a marked sodium diuresis and potassium retention with return of serum sodium and potassium values to normal. Blood pressure became normal. Polyuria and polydipsia disappeared, although renal concentrating ability returned only slowly. Bioassays for urinary sodium-retaining corticoid were normal postoperatively. The patient became entirely asymptomatic.

Analyses of muscle biopsies, removed at operation showed a great excess of intracellular sodium and marked decrease in intracellular potassium. Bioassay of the tumor removed showed large amounts of sodium-retaining corticoid compared to normal adrenal tissue.

CORTELL

HYPERTENSION

D'Alonzo, C. A., Fleming, A. J. and Gehrmann, G. H.: Role of Heredity in the Problem of Hyper-

tension in Industrial Workers. J. A. M. A. **157:** 631 (Feb. 19), 1955.

In this study, 799 DuPont Company employees, 40 years of age and over, were selected at random. They were given complete physical examinations each year. Progressive or constant changes in blood pressure with eyeground and electrocardiographic correlation were available, in many instances dating back from five to 25 years. All these employees were available for additional study and questioning and supplied "good" family histories. These histories proved important. Where the parents, particularly the mother, were known to have a cardiovascular disease, the prevalence of high blood pressure was greater than in employees whose parents did not have a cardiovascular disease. The findings suggest that a knowledge of family history might prove of value in such matters as job placement, in relation to the present or future physical capacity of employees and in the followup modification and possible prevention of this important disease. Susceptible employees should be spotted before the onset of hypertension and attempts should be made to modify or prevent the processes, thought to be contributing factors.

KITCHELL

Rothman, S.: Mechanisms Responsible for the Elevated Blood Pressure in the Cerebral Hypertensive Rabbit. Am. J. Physiol. **180:** 61 (Jan.), 1955.

Cerebral hypertension was produced in rabbits by bilateral ligation of the internal and external carotids. Evidence from these experiments supports the theory that hypertension in the cerebral hypertensive rabbit depends on an increased sympathetic activity with an increased production of norepinephrine.

OPPENHEIMER

Hughes, W. M., Dennis, E. and Moyer, J. H.: Treatment of Hypertension with Oral Reserpine Alone and in Combination with Hydralyzine or Hexamethonium. Am. J. M. Sc. **229:** 121 (Feb.), 1955.

The blood pressure responses of 67 patients, treated with oral reserpine alone, revealed that 43 per cent were improved by this agent, with 12 per cent becoming normotensive. Six patients were maintained on this drug alone for a year or more with no evidence of tolerance being manifested. Reserpine was used in combination with hydralazine in 15 patients, 14 of whom were resistant to reserpine alone. Of this group 87 per cent showed a significant drop in blood pressure, with 33 per cent becoming normotensive. The usual side effects of Apresoline were not prominent when this drug was added to the reserpine program. This observation suggested that the undesirable effects of hydralazine can be prevented by reserpine. The combination of hexamethonium and reserpine was employed in 32 patients, 27 of whom had been treated unsuccessfully with the latter agent alone. The combined therapy was effective in 84 per cent, with 47 per cent of the group becoming normotensive. The dosage requirements and side effects of hexamethonium were reduced when combined with reserpine; in addition, the blood pressure response was more stable. Constipation occurred frequently but was controlled easily with laxatives. Observations on renal hemodynamics indicated that there was a tendency to a reduction in glomerular filtration rate and a variable effect on renal blood flow was noted. This indicates that the improvement in clinical status was probably attributable to improved renal function but may be a direct result of blood pressure reduction.

SHUMAN

Imber, I. and Clymer, R. H., Jr.: Obstruction of the Renal Artery Producing Malignant Hypertension. New England J. Med. **252:** 301 (Feb. 24), 1955.

Preoperative studies in a 34 year-old man disclosed hypertension of less than one year's duration, hypertensive retinopathy, persistent albuminuria, elevation of the blood urea nitrogen and a urine of low specific gravity. Abdominal aortography disclosed a vascular abnormality of the right renal artery. Although impaired, the right kidney did have some function. A nephrectomy was performed and the right renal artery was found to be distorted and constricted by a fibrous band. The right kidney was found to be morphologically normal and there was no intrinsic disease of the renal artery. Operation was followed by return of renal function to normal, clearing of all symptoms and a slow recovery of concentrating power; this sequence together with the preoperative elevation of nitrogen is said to be suggestive of tubular impairment. Thus the diminution of function in the contralateral, normal kidney proved reversible. The short duration of the preexisting hypertension is considered a major factor in the excellent response to removal of the offending kidney. This case is considered to provide additional evidence that a diminished blood flow in a major renal artery may cause hypertension and impairment of total renal function.

ROSENBAUM

PATHOLOGIC PHYSIOLOGY

White, A. G., Entmacher, P. S., Rubin, G. and Leiter, L.: Physiological and Pharmacological Regulation of Human Salivary Electrolyte Concentrations; with a Discussion of Electrolyte Concentration of Some Other Exocrine Secretions. J. Clin. Invest. **34:** 246 (Feb.), 1955.

The electrolytes of saliva were studied in 73 normal subjects under standardized conditions. Daily injections of desoxycorticosterone acetate in oil led to a decrease in chloride and an increase in potassium concentration. Pilocarpine, given sub-

cutaneously, increased sodium and decreased potassium concentration. Administration of a mercurial diuretic produced no statistically significant changes in salivary electrolytes.

From their detailed studies the authors conclude that reabsorption of sodium and chloride by rodded epithelium in excretory ducts leads to hypotonicity of these electrolytes in saliva. The potassium level in saliva is higher than that of serum, probably because of active secretion of potassium by the gland.

WAIFE

Tourman, P. and Hervey, G. R.: An Experimental Study of Oedema in Potassium Deficiency. Clin. Sc. **41:** 75 (Feb.), 1955.

A 28 year-old subject was depleted of potassium by means of a deficient diet and supplements of an ammoniated resin. While taking the resin he lost 2 Kg. in weight. Associated with the potassium depletion were the usual signs: anorexia, weakness, depression of T waves and appearance of U waves in the electrocardiogram. After the resin was stopped and 256 mEq. of sodium and chloride were added to his diet he gained 4 Kg. and showed edema of the eyes and later the ankles. The depletion period produced a net loss of 470 mEq. of potassium while only 2 Kg. of weight was lost. It was calculated that after six days of sodium chloride, the volume of blood and extracellular fluids had expanded by about 15 and 18 parts per 100 respectively. The expansion of the latter accounted for the weight gain. The mechanism underlying the retention of sodium is not known, but a probable cause may be the liberation of an aldosterone-like steroid from the adrenals.

ENSELBERG

Oliver, M. F. and Boyd, G. S.: Plasma Lipid and Serum Lipoprotein Patterns During Pregnancy and Puerperium. Clin. Sc. **14:** 15 (Feb.), 1955.

Circulating lipids were studied at fortnightly intervals from the ninth week to term in a group of 12 normal primigravidae aged 18 to 31. Blood samples were also drawn during labor and in the puerperium. These studies clearly demonstrated a rise in plasma total cholesterol as well as ester and free cholesterol. This rise reached a peak between the thirty-first and thirty-third weeks when the levels increased 50 per cent above the starting values. In addition, the plasma phospholipids and the plasma total cholesterol phospholipid ratio increased both about 25 per cent in the same time. The distribution of cholesterol between the serum α and β lipoproteins rose very significantly.

These changes bear a striking similarity to the pattern associated with overt coronary sclerosis. The authors discuss the intricate hormonal and metabolic influences which may be responsible for these changes and indicate the need for further study. One implication of the findings is that frequent episodes of this "coronary pattern," as it occurs in multiple pregnancies, might be harmful to the arterial intima.

ENSELBERG

Barger, A. C., Wilson, G. M., Price, H. L., Ross, R. S., Brooks, L. and Boling, E. A.: Relationship Between Exchangeable Sodium and Rate of Sodium Excretion in Dogs With Experimental Valvular Lesions of the Heart. Am. J. Physiol. **180:** 387 (Feb.), 1955.

Although either tricuspid or pulmonary insufficiency reduce the rate of sodium excretion, a slight rise or no alteration is observed in the amount of exchangeable sodium in the body. These small changes in body sodium and rate of excretion of sodium load were unrelated. Combined tricuspid insufficiency and pulmonary stenosis caused a marked reduction in sodium excretion and ascites developed. Body sodium and sodium excretion was unaffected by pulmonary stenosis and sham surgery on myocardium and pericardium. It is apparent that there were no changes in the ability to excrete a sodium load even though there were little or no changes in total body sodium. The injected sodium was not diluted by an increased pool of body sodium and hence this could not explain the reduced sodium excretion rate.

OPPENHEIMER

Oard, H. C. and Walker, G. I., Jr.: Clinical Management of the Anuric Patient. Am. J. Med. **18:** 199 (Feb.), 1955.

Urging minimal intervention in the treatment of patients with acute reversible anuria and oliguria, the authors present four cases of acute and severe oliguria resulting from carbon tetrachloride intoxication, incompatible transfusion and shock, associated with postpartum hemorrhage. Each patient recovered under treatment during the oliguric phase which consisted of a minimal intake of 20 per cent lactose solution; this was administered orally in a total daily intake of about 500 cc. to provide restricted fluid and palatable carbohydrate without protein. The patient's thirst determined the daily intake of fluid. No attempt was made to replace or alter electrolytes during the period of oliguria. The patients progressed to diuresis in 9, 10, 12 and 16 days respectively. Subsequent studies disclosed apparent recovery of the renal lesions. The extremely low fluid intake maintained adequate hydration as evidenced by clinical evaluation and by repeated blood volume determinations in one patient. The regimen was successful under extremely variable environmental conditions.

HARRIS

Parrish, A. E., Rubenstein, N. H. and Howe, J. S.: Acute Renal Insufficiency Associated with

Respiratory Infections. Am. J. Med. **18:** 237 (Feb.), 1955.

The authors present three cases with uremia due to acute renal insufficiency associated with acute pulmonary infections. Renal biopsies showed marked tubular damage which was reversible and glomerular damage which improved but did not entirely disappear. The etiology of these changes is obscure but appears related to a combination of alcoholism, pulmonary infection and dehydration.

HARRIS

Lyons, H. A., Zuhdi, M. N. and Kydd, D. M.: The Effects of Carbonic Anhydrase Inhibitor on Arterial Blood Gases in Chronic Pulmonary Emphysema: A Preliminary Report. Am. J. M. Sc. **229:** 193 (Feb.), 1955.

Diamox was administered in doses of 250 mg. twice daily to nine patients with pulmonary emphysema during which the effects of the agent upon arterial blood gases was studied. The most significant effect was a decrease in the arterial partial pressure of carbon dioxide in six patients. In four patients, clinical improvement consisted of easier breathing, better appetite and loss of drowsiness. There was no correlation between the arterial partial pressure of carbon dioxide and of oxygen responses to Diamox. There was no measureable effect of this agent upon pulmonary hemodynamics, cardiac output or pulmonary ventilatory or respiratory determinations. The explanation for clinical improvement may lie in the mobilization of storage reservoirs of carbon dioxide, although no measurement of total carbon dioxide exchange was employed.

SHUMAN

Holman, E.: The Obscure Physiology of Poststenotic Dilatation: Its Relation to the Development of Aneurysms. J. Thoracic Surg. **28:** 109 (Aug.), 1954.

The author investigated the forces responsible for poststenotic dilatation, seen clinically in the subclavian artery beyond a congenital cervical rib, in the aorta beyond a subaortic stenosis, in the pulmonary artery beyond a congenital stenosis of the pulmonary valve and in the descending aorta beyond a coarctation.

Using an artificial circulatory system, the author performed experiments which support the view that poststenotic dilatation is the direct effect of the play of hydraulic forces set in motion by the stenosis, and that it varies in degree with the pressure and velocity with which fluid is ejected from the stenotic channel. He also found that there is a critical level of pressure and velocity below which poststenotic dilatation does not occur. Other factors which affect the change are the inherent resistance of the vessel wall to dilatation and the relationship between the elasticity of the wall and the pressure and velocity of flow to which it is subjected.

Once a dilatation has been initiated, the process is perpetuated and enhanced through the application of the principle that a widened lumen slows the stream; a slowing of the stream increases lateral pressure; increasing lateral pressure further dilates the vessel.

ABRAMSON

Rosin, H. and Farah, A.: Post-Stimulation Potentiation of Contractility in the Isolated Auricle of the Rabbit. Am. J. Physiol. **180:** 75 (Jan.), 1955.

When contractions were elicited following a period of stimulation at a frequency higher than the control rate of the electrically driven atria or ventricle, a potentiation of contraction could be demonstrated. The authors have postulated a hypothetic potentiating substance. This material is considered to have been produced during stimulation. It is utilized during contraction.

OPPENHEIMER

Kaye, M.: The Effect of a Single Oral Dose of the Carbonic Anhydrase Inhibitor, Acetazoleamide, in Renal Disease. J. Clin. Invest. **34:** 277 (Feb.), 1955.

A single oral dose of acetazoleamide (Diamox), about 10 mg. per Kg., was given to four normal controls and 15 patients with renal disease. A diuresis, consisting of an increase in urine volume, sodium, potassium and bicarbonate, was produced in normals and, to a lesser extent, in patients with renal disease without acidosis. These changes were minimal or absent in acidotic subjects.

No evidence of untoward effect was seen in urine, blood pressure or degree of azotemia after use of this drug.

WAIFE

Sullivan, W. J. and Dorman, P. J.: The Renal Response to Chronic Respiratory Acidosis. J. Clin. Invest. **34:** 268 (Feb.), 1955.

When increased carbon dioxide tension exists in body fluids, there is an increase in base, bound to bicarbonate. This elevated plasma bicarbonate concentration is maintained by an enhanced rate of renal tubular reabsorption of bicarbonate.

Data obtained from experiments on dogs reveal that in acute respiratory acidosis the magnitude of the enhanced tubular reabsorption is not sufficient to account for the elevated plasma levels often found in chronic carbon dioxide retention in man.

It is suggested that during the first 48 hours of chronic respiratory acidosis some adaptation mechanism develops, probably involving hydrogen ion secretion, which alters the kinetics of the reactions concerned. This may involve the adrenal cortex.

WAIFE

Eskola, O., Koskelo, P. and Halonen, P. I.: Increased Urinary Coproporphyrins following Acute

Myocardial Infarction and Pulmonary Embolism. Am. Heart J. **49:** 258 (Feb.), 1955.

The authors have studied the secretion of coproporphyrins in the urine in 12 cases of myocardial infarction, five cases of pulmonary embolism and 12 healthy persons. In the healthy subjects, the daily amount of urinary coproporphyrins was 21 to 142 μg. During the first two or three days following myocardial infarction and pulmonary embolism an increase occurred in the daily urinary coproporphyrin secretion, the total amount being 310 to 207 μg. per 24 hours in the patients with infarction and 287 to 203 μg. per 24 hours in patients with pulmonary embolism.

RINZLER

Albrink, M. J., Man, E. B. and Peters, J. P.: The Relation of Neutral Fat to Lactescence of Serum. J. Clin. Invest. **34:** 147 (Feb.), 1955.

A quantitative study was made of the relationship between serum neutral fat and cloudy sera. Neutral fat was the only lipid which was consistently associated with lactescence, which invariably was present when neutral fat exceeded 20 mEq. per liter.

The insoluble material causing lactescence was composed chiefly of neutral fat, but also included considerable quantities of cholesterol and phospholipid.

From these ultracentrifugal studies on solubility, the authors postulate that the primary defect in lactescence is in the removal of soluble neutral fat from serum. Neutral fat is probably delivered to the serum chiefly in the insoluble form but is early converted to the soluble state. A limitation exists in the maximum quantity of soluble neutral fat in the serum. If a block exists in the removal of this material, more and more insoluble neutral fat would accumulate.

It is also possible that cholesterol and phospholipid are dissolved in the insoluble neutral fat particles. This might explain why the solubility of these substances was decreased when neutral fat increased.

WAIFE

Bellville, J. W., Artusio, J. F., Jr. and Glenn, F.: The Electroencephalogram in Cardiac Arrest. J. A. M. A. **157:** 508 (Feb. 5), 1955.

The authors present two well documented cases of primary cardiac arrest in patients undergoing mitral valvuloplasty where the electrocardiogram and the electroencephalogram have been monitored by means of continuously recording instruments. It appears that the electroencephalogram is a more sensitive indicator of hypoxia, depth of anesthesia, and hypercapnia than are clinical signs.

KITCHELL

Russek, H. I., Zohman, B. L. and Dorset, V. J.: Effects of Tobacco and Whiskey on the Cardiovascular System. J. A. M. A. **157:** 563 (Feb. 12), 1955.

It is common practice for a physician to advise against the use of tobacco in all patients suffering from angina pectoris, but there is still considerable difference of opinion as to whether or not the use of tobacco is harmful to patients with coronary artery disease. Observations were made on 65 subjects. Of this number, 28 were normal, but all were habitual smokers. Nine of these normal subjects had sought medical aid because of persistent precordial discomfort; the remaining 19 were selected from a group of 96 healthy persons because they claimed cerebral, cardiac, or gastro-intestinal symptoms on smoking. There were 37 patients with coronary artery disease. Six were nonsmokers, 10 smoked occasionally and 21 were heavy smokers. All 65 subjects made 284 smoking tests. Each test was carried out after a 30-minute rest period with the subject in the recumbent position on the ballistocardiograph table. The individual being tested had not smoked for at least two hours before the test. When blood pressure and pulse rate had reached steady values, a control electrocardiogram and ballistocardiogram were taken. A cigarette was then smoked, with the subject puffing at his habitual rate and inhaling, or not, as was his custom. Electrocardiograms and ballistocardiograms were made at frequent intervals after the completion of smoking; a careful record was kept of the blood pressure and heart rate during this period. The brands of regular cigarettes varied according to the taste of the smoker. Only one kind of "denicotinized" cigarette was employed and was purchased on the open market.

There was a significant increase in heart rate and blood pressure following the smoking of a regular cigarette in both the normal subjects and patients with coronary heart disease. Sixteen of the 28 normal patients had significant electrocardiographic alterations. Eighteen of the 37 patients with coronary disease showed deteriorations in the ballistic pattern following the smoking of a regular cigarette. Concomitant electrocardiographic alterations seen in these subjects were relatively slight. "Denicotinized" cigarettes showed no superiority over regular brands as measured ballistocardiographically. The observed effects of glyceryl trinitrate and whiskey, respectively, on the ballistic response to smoking appear to indicate that the nicotine response is based primarily on peripheral vascular constriction and not alterations in coronary blood flow. Some have recommended simultaneous indulgence in alcohol and tobacco on the theory that the "coronary vasodilator" effects of the former may counteract the "coronary vasoconstrictor" effects of the latter. Unfortunately, there is as little valid evidence that alcohol increases coronary blood flow as there is that tobacco reduces it.

KITCHELL

Buff, I.: Effect of Cigarette Smoking in the Normal Person. J. A. M. A. **157:** 569 (Feb. 12), 1955.

There are few objective methods that attempt to register the effect of tobacco on the human heart. One of the simplest methods of study is by use of the ballistocardiograph. Four hundred normal persons were tested, (150 women and 250 men); all were under 40 years of age. It is significant to note that most persons under 40 without cardiac disease have normal ballistocardiograms. The patient was first tested at least two hours after smoking a cigarette, then at 5 and 10 minute intervals after smoking. Tracings, showing small changes, were considered of little consequence. Only the ballistocardiograms that were definitely and without question abnormal were considered abnormal. Of the entire 400 ballistocardiograms of normal persons, 42 were abnormal (about 10 per cent). Persons who have an abnormal ballistocardiographic tracing after smoking should not continue to smoke. The author hopes to follow these cases who are sensitive to tobacco to determine whether or not coronary artery disease will develop in them in the future.

KITCHELL

Wood, F. J. Y.: Ammonium Chloride Acidosis. Clin. Sc. **41:** 81 (Feb.), 1955.

A normal subject was given 8 Gm. ammonium chloride daily in divided doses over a continuous period of 44 days. Considerable acidosis developed, reaching its peak in five days when the blood pH fell to 7.33 and the plasma bicarbonate to 19.8 mEq., while the chloride rose to 115 mEq. per liter. The acidosis then subsided to a lower level (pH 7.34) and remained there during the whole period of administration of ammonium chloride. Upon cessation of the drug the acidosis was quickly succeeded by alkalosis for a few days.

The extra chloride was excreted at first with sodium, then with potassium; by this mechanism, the body's loss of sodium reserves was limited. After five days, the kidney's production of ammonia became sufficient to neutralize the extra chloride, eliminating the need for sodium and potassium for this purpose. Hence the plasma pH, bicarbonate and chloride partly returned to their normal values. This new equilibrium was maintained as long as ammonium chloride was given. When it was stopped, renal production of ammonia returned slowly to normal. During this period, because of the availability of base, an alkalosis appeared and the remainder of the "borrowed" sodium and potassium returned to the body's stores. Then ammonia production fell below normal. The author stresses the importance of the finding that the acidosis continued during the whole period of administration of ammonium chloride.

ENSELBERG

Moses, C.: Effect of Oral Inositol Phosphatide on Development of Experimental Atherosclerosis. Geriatrics **9:** 325 (July), 1954.

The oral administration of 100 ml. of two per cent inositol phosphatide, three times a week, to male, albino rabbits, receiving a high cholesterol diet, failed to decrease the occurrence of aortic atherosclerosis or to influence the weight gain, cholesterol partition, cholesterol to lipid phosphorus ratio, urea nitrogen, total protein or hematocrit in animals followed-up for 4, 8 and 12 weeks.

BERNSTEIN

Gorlin, R.: The Mechanism of the Signs and Symptoms of Mitral Valve Disease. Brit. Heart J. **16:** 375 (Oct.), 1954.

The author believes that an understanding of the pathologic physiology of mitral disease will lead to a proper interpretation of its clinical manifestations. The amount of pressure necessary to force a given amount of blood through an orifice depends upon its size. As the normal mitral area of 5 cm.^{2} decreases to less than 1 cm.^{2}, a low normal rate of 150 ml. per second is barely tolerated. With tachycardia and systolic time, therefore, cardiac output is reduced unless the elevated left atrial pressure is further increased with consequent production of increased dyspnea or pulmonary edema. A relationship is therefore found between height of pulmonary capillary pressure and pulmonary edema and between degree of stenosis and severity of dyspnea. With time, organic changes occur in the pulmonary end arteries with increased pulmonary vascular resistance. Right ventricular pressure increases. When the right ventricle finally dilates, congestive failure appears.

If the cardiac output is normal in pure mitral insufficiency, no symptoms are present. If the cardiac output is decreased with normal left ventricular end diastolic pressure, fatigue is present. If the left ventricular end diastolic pressure is increased, left heart failure simulating that observed in mitral stenosis is present.

Stenosis is moderate (1.5 to 2 cm.^{2}) in combined mitral stenosis and insufficiency. Stenosis limits flow through the mitral valve and left ventricular output is decreased because of the leak. Fatigue is therefore the dominant symptom. Smouldering carditis is invoked to explain left ventricular failure. Again, in these instances, the clinical picture resembles that of pure advanced mitral stenosis.

SOLOFF

Abelmann, W. H., Kowalski, H. J. and McNeely, W. F.: Cardiovascular Studies During Acute Infectious Hepatitis. Gastroenterology **27:** 61 (July), 1954.

Cardiac output, direct arterial pressure and oxygen consumption were measured at rest in 10 patients convalescing from acute infectious hepatitis

These observations were repeated during mild to moderate exercise in nine patients. At rest, some patients showed a relatively slow heart rate, while the blood pressure and blood flow were within normal limits. During exercise the heart rate and the cardiac output increased in every instance, while peripheral vascular resistance decreased. The response to exercise was considered entirely normal.

BERNSTEIN

PHARMACOLOGY

Finnegan, T. R. L. and Trounce, J. R.: Depression of the Heart by Quinidine and its Treatment. Brit. Heart J. **16:** 341 (Oct.), 1954.

Of 115 individuals receiving quinidine, the authors found one fatal reaction, two severe reactions characterized by a fall in blood pressure, collapse and convulsions and five minor reactions such as sinoatrial block, prolonged P-R interval, widening of the QRS complexes and ventricular premature beats.

Studies in the isolated rabbit heart and the anesthetized rabbit indicate that harmful effects of quinidine are due to its depressant action on conduction, myocardial contraction and respiration and at times due to the production of ventricular fibrillation. Adrenalin, intravenously, is the most effective agent in combating depression due to quinidine.

It is suggested that the effects on man of quinidine and its antagonist, adrenalin, are similar.

SOLOFF

Bronsky, D., Dubin, A. and Kushner, D. S.: Diuretic Action of Benemid. Its Effect upon the Urinary Excretion of Sodium Chloride, Potassium and Water in Edematous Subjects. Am. J. Med. **18:** 259 (Feb.), 1955.

In 13 subjects with uncomplicated congestive heart failure, Benemid in doses of 4 Gm. daily produced a significant diuretic response in most instances on the first or second day of drug administration. The mean increment of water excreted on the day of maximal response was 1,330 cc., of sodium 91 mEq. and of chloride 76 mEq. per 24 hours. Water diuresis without enhancement of sodium or chloride excretion occurred in seven other subjects. Failure of diuresis to occur in the remaining five subjects was associated with the presence of hepatic disease, renal disease, hyponatremia and hyponatruria. It is postulated that Benemid-induced diuresis is the result of decreased tubular reabsorption of water, sodium and chloride.

HARRIS

Kalmanson, G. M., Drenick, E. J., Binder, M. J. and Rosove, L.: Pentaerythritol Tetranitrate in the Treatment of Angina Pectoris. Arch. of Int. Med. **95:** 819 (June), 1955.

The effect of pentaerythritol tetranitrate on angina pectoris was studied in 23 patients by alternating placebo medication with the drug, using the "double blind" method. This study failed to demonstrate any beneficial effect of this drug on angina pectoris.

BERNSTEIN

Holti, G.: Measurements of the Vascular Responses in Skin at Various Time Intervals after Damage with Histamine and Ultra-Violet Radiation. Clin. Sc. **41:** 143 (Feb.), 1955.

Bloodflow changes were studied in skin injured by histamine and by ultra-violet irradiation. It was found that skin which has been strongly whealed by histamine or which has reacted intensely to ultra-violet radiation shows two long-lasting vascular abnormalities: (1) an increased capacity of minute vessels to dilate in response to stimuli such as histamine or heat and a diminished capacity to contract in response to epinephrine or cold and (2) a reduction in whealing response to histamine.

These changes persist for 3 to 8 weeks after the histamine injury, and for six months or longer after ultra-violet irradiation. These prolonged after-effects, following two different types of injury, are probably due to independent changes in permeability and in vasomotor tone. It is possible that some of the changes are due to the continuous release of a substance from damaged epidermal cells.

ENSELBERG

DiPalma, J. R.: The Pharmacology of N-(4-Metholybenzl)-Isoquinolinium Chloride, WIN 2173, With Particular Reference to its Cardiac Effects. J. Pharmacol. & Exper. Therap. **113:** 125 (Feb.), 1955.

This compound, WIN 2173, has antifibrillatory properties but does not depress the excitability of the myocardium or prolong the refractory period as do quinidine and procaine amide. It is being tried clinically as a cure for human arrhythmias. This drug is an aromatic quaternary ammonium compound, which caused the following changes. In both animals (dogs and cats) and man, it transiently increased pulse rate. In animals, the blood pressure transiently dropped, but this parameter did not change in man. There were no electrocardiographic changes in man. The amplitude and rate of isolated cat atrial contraction increased. Cooling of the atrium to 18 to 24 C. increased this effect. The refractory period was increased only after very high doses, which are above the dose that stimulates the rate and amplitude of the atrium. This drug was shown to be more potent than quinidine in raising the threshold of electrically induced atrial fibrillation in cats. In inducing arrhythmias by epinephrine and petrolatum ether, this drug did not protect the cats, as did procaine amide and curare.

Intravenous WIN 2173, at high doses, was shown

to block ganglia by the cessation of contractions of the cats' nictitating membrane even with stimulation of the sympathetic trunk. It was concluded that it is a weak ganglionic and neuromuscular blocking agent.

Intravenous or intramuscular doses below 5 mg. per kg. of body weight were well tolerated in unanesthetized humans and animals. Transient pupillary dilation, flushing and vertigo occurred.

WECHSLER

Marshall, J. M.: Action of Iodoacetic Acid, 2,4 Dinitrophenol, and *L*-Triiodothyronine on the Electrical Response of the Myocardium. Am. J. Physiol. **180:** 350 (Feb.), 1955.

Data from these experiments indicate that electric properties of heart muscle are changed in a characteristic manner which is determined by the site in the metabolic chain at which the inhibitor acts. Iodoacetic acid produces an irreversible block of the glycolytic chain by inhibiting triphosphate dehydrogenase. This material both aerobically and anaerobically decreased the refractory period, Q-T interval and latency, combined with marked depression of S-T segment. Adenosine triphosphate did not reverse these effects. Dinitrophenol is stated to uncouple aerobic oxidation and production of energy rich phosphates. Dinitrophenol increased refractory period and latency but decreases Q-T. Adenosine triphosphate restored the refractory period briefly to normal but had only a minor action on the other properties. L-triiodothyronine, which acts in a metabolic manner similar to dinitrophenol, was observed to produce results similar to those of dinitrophenol in most cases although Q-T was increased and adenosine triphosphate ineffective.

OPPENHEIMER

Hilton, J. G.: Effects of Graded Doses of Epinephrine and of Nor-Epinephrine Upon the Isolated Perfused Rabbit Heart. Am. J. Physiol. **180:** 371 (Feb.), 1955.

Rabbits' hearts perfused with Locke's Solution were the test objects. In low doses, both epinephrine and norepinephrine increase the inotropic action. Differences between the two drugs were not marked. At higher doses, there were some cases in which the response to the second and higher dose was less than that to the immediately preceding smaller one. This was more marked with norepinephrine than with epinephrine. Effects on rate with each drug were similar to those on the force of contraction. Duration of inotropic effects were much longer in the case of epinephrine.

OPPENHEIMER

Hendley, E. D. and Schiller, A. A.: Protection Against Hypoxemic Edema by Histaminic and Adrenergic Blockade. Am. J. Physiol. **180:** 378 (Feb.), 1955.

These experiments represent an evaluation of the factors of decreased vascular resistance and true alteration in structural integrity of capillaries as they pertain to increased capillary permeability during hypoxemia. Dibenzyline decreased vasomotor resistance to the same level in mild and severe hypoxemia of perfused rat hind limbs. In severe hypoxemia, the rate of edema formation was slower with dibenzyline than in untreated controls, even though capillary pressure and flow were high. Dibenzyline seems to prevent increased capillary permeability during severe hypoxemia. Neo-antergan gave similar results but was somewhat less effective.

OPPENHEIMER

Bean, J. W. and Johnson, P. C.: Epinephrine and Neurogenic Factors in the Pulmonary Edema and CNS Reactions Induced by Oxygen at High Pressure. Am. J. Physiol. **180:** 438 (Feb.), 1955.

Normal and adrenalectomized rats were exposed to oxygen at 80 lb. gage pressure. Subcutaneous epinephrine given before exposure increased the deleteriois effects of oxygen at high pressure. Neuromuscular reactions, mortality and gross pulmonary damage, due to oxygen at high pressure, were all increased in both normal and adrenalectomized animals. Thus, adrenal cortex is not essential for the effect of epinephrine in augmenting the adverse actions of oxygen under high pressure. It is considered that a part of the undesirable actions of oxygen at high pressure in intact animals is due to increased release of epinephrine. Oxygen at high pressure and epinephrine produce similar pulmonary damage. They may be synergistic and possibly act by a common mechanism. It is pointed out that former reports on the protective action of adrenalectomy against oxygen at high pressure were probably due more to the removal of medulla than of cortex. Sympathetic nervous components and, possibly, those of hypothalamic origin also play a role in pulmonary damage due to oxygen at high pressure.

OPPENHEIMER

Hall, B.: Recovery of Patient in Prolonged Shock After Arterenol Therapy. J.A.M.A. **157:** 653, (Feb. 19), 1955.

Since 1948, when *l*-arterenol became available, there have been reports of its value in the treatment of shock. The reported case of prolonged shock, following surgery to the common duct, necessitated intravenous therapy with arterenol over a total of 22 days. A total of 1,452 mg. of arterenol base in about 115 L. of fluid was required. Full recovery was complicated by a large skin ulceration at the site of a subcutaneous extravasation of the drug. To date, this is the longest duration of therapy and the largest total dosage of *l*-arterenol described.

KITCHELL

Donegan, C. K. and Townsend, C. V.: Phenylephrine Hydrochloride in Paroxysmal Supraventricular Tachycardia. J.A.M.A. **157:** 716, (Feb. 26), 1955.

Phenylephrine (Neo-Synephrine) hydrochloride was first suggested for the treatment of paroxysmal supraventricular tachycardia by Youmans and his group in 1947. It has been felt that the drug was relatively innocuous in the absence of heart disease but dangerous in the presence of heart disease. The authors report a case of paroxysmal supraventricular tachycardia associated with coronary artery disease that was refractory to the usual drugs used in the treatment of this disorder. Phenylephrine (Neo-Synephrine) hydrochloride proved effective but also it produced short runs of ventricular tachycardia which support the idea that it must be regarded as a potentially dangerous agent and must be used with caution.

KITCHELL

Kleeman, C. R., Bass, D. E. and Quinn, M.: Effect of 6063, Sodium Bicarbonate and Ammonium Chloride on Electrolyte Composition of Thermal Sweat. Proc. Soc. Exper. Biol. & Med. **88:** 253 (Feb.), 1955.

Four normal adult males were subjected to room temperatures maintained at 120 F. (dry bulb) and 93 to 95 F. (wet bulb) for one to one and one-half hours. During this time, sweat was collected from the arms and hands. The test substances were ingested for two days prior to the collection of sweat. The sweat was analyzed for ammonia, titratable acidity, pH, total carbon dioxide content, lactate, sodium, potassium and chloride. Urine and blood collected during the experimental period were similarly analyzed. In contrast to the marked changes in urinary composition and the pH following ingestion of 6063 (carbonic anhydrase inhibitor), ammonium chloride and sodium bicarbonate, no consistent relationship between acid-base balance of body fluids and the ammonia, titratable acidity, pH or lactic acid of sweat was demonstrated. The collected sweat was a moderately acid secretion, low in ammonia and titratable acid and of poor buffering capacity. Sweat maintained these characteristics, regardless of the substance ingested or the alteration in acid-base balance produced, indicating that sweat glands have no regulatory role in the maintenance of hydrogen ion concentration of body fluids.

CORTELL

Davison, S., Borken, N. and Wolf, M.: Elevations in Temperature of Joint, Muscle and Skin, Following Injection of Priscoline Intra-arterially. J. Mt. Sinai Hosp. **21:** 98, (July–Aug.), 1954.

Following the femoral intra-arterial administration of Priscoline, simultaneous skin, muscle and intra-articular temperatures were determined in the ipsolateral knee in nine normal subjects. In 7 of the 9, distinct skin, muscle and intra-articular temperature elevations were noted. In the remaining two subjects, the initial joint and muscle temperatures were already over 98 F. and a further increase was probably precluded. In three subjects, normal saline was initially injected intra-arterially. In no instance was there an alteration in temperature. It is suggested that vasodilating drugs such as Priscoline do not necessarily divert blood flow from deep structures to the skin. Studying the temperature changes reported above, it is conceivable that the injection of a vasodilating drug intra-arterially produces a direct concentration in and about a joint and effectively increases local blood flow.

BERNSTEIN

Moyer, J. H., Handley, C. A., and Seibert, R. A.: Effect of Adrenergic Blockade on Renal Hemodynamics and Excretion of Water and Electrolytes. Am. J. Physiol., **180:** 146, (Jan.), 1955.

The dihydrogenated, ergot derivative, Hydergine, increases sodium and water excretion. Hydralazine decreases sodium and water excretion. In each case, there is a central action which produces hemodynamic changes. Adrenergic blocking agents (phenoxybenzamine, phentolamine) do not change sodium and water excretion. Excretion rate of sodium and water by the kidney seems to be independent of chemical blockade of renal nerves.

OPPENHEIMER

PHYSICAL SIGNS

Wehrmacher, W. H.: Significance of Tietze's Syndrome in Differential Diagnosis of Chest Pain. J.A.M.A. **157:** 505 (Feb. 5), 1955.

Tietze's syndrome, a painful, benign, nonsuppurative swelling of the costochondral or the sternoclavicular junction, was originally described over 30 years ago in Germany. Foreign reports of over 100 cases indicate its importance in the differential diagnosis of chest pain. The author reports four cases which demonstrate the occurrence of the syndrome in the United States. Tietze's syndrome should be given routine consideration by the physician when he is evaluating pain in the chest. It is important that the patient with this syndrome be reassured of the benign character of the disorder.

KITCHELL

Millikan, C. H. and Siekert, R. G.: Studies in Cerebrovascular Disease. I. The Syndrome of Intermittent Insufficiency of the Basilar Arterial System. Proc. Staff Meet., Mayo Clin. **30:** 61 (Feb.), 1955.

Ten cases have been reported in which strange intermittent attacks were characterized by symptoms which indicated transitory impairment of function in some portion of the pons, mesencephalon or occipital lobes. In three cases the clinical picture

of thrombosis of the basilar artery developed subsequently. The latter diagnosis was confirmed at necropsy. It is suggested that these strange attacks are a result of temporarily inadequate blood flow through the basilar arterial system and that the occurrence of such episodes should be called the "syndrome of intermittent insufficiency of the basilar arterial system." Experience indicates that the attacks terminate with administration of anticoagulant drugs.

SIMON

Richards, M. R., Merritt, K. K., Samuels, M. H., and Langmann, A. G.: Frequency and Significance of Cardiac Murmurs in the First Year of Life. Pediatrics **15:** 169 (Feb.), 1955.

This report, of the presence and significance of heart murmurs in the first year of life, is from a comprehensive study the authors have completed on a group of 5,017 infants. Other reports, dealing with other features of this same group of infants, have been made and one is reviewed above. Statistically, the study is sound. In the immediate post-natal period a murmur was heard in 1.7 per cent of the infants, but on repeated examinations at 6 and 12 months the incidence rose to seven per cent. Of the 353 murmurs heard in full term infants, only 23 were determined to be organic murmurs. It is the authors' opinion that a murmur heard at birth carries a 1:12 probability of congenital heart disease. heard again at six months, a 1:3 chance and if it persists to 12 months, the chance is 3:5 that congenital heart disease is present.

HARVEY

Apley, J. and Perry, C. B.: A Six-Year Survey of the Cases Seen at a School Cardiac Clinic. Arch. Dis. Child. **29:** 317 (Aug.), 1954.

An analysis was made of 1,286 children referred, from 1943 to 1948, to a cardiac clinic for school children. Past or present rheumatic heart disease was diagnosed in 148, 103 were diagnosed as having congenital heart disease (95 acyanotic) and a "functional" murmur was diagnosed in 303 children.

BERNSTEIN

Barritt, D. W.: Simple Pulmonary Stenosis. Brit. Heart J. **16:** 381 (Oct.), 1954.

The author reveiws simple pulmonary stenosis in 33 cases (16 males, 17 females) to more clearly define the natural history of this disease.

Nine cases occurred in the first decade, 15 in the second and nine in the third. While 23 had no symptoms, six were genuinely breathless and three were handicapped. Body build was normal in all cases. The cardiac impulse was normal in 22. Eleven had a right ventricular lift in the third left interspace. All had a pulmonary systolic thrill. The second heart sound was split in 11. Poststenotic dilatation of the pulmonary artery was marked in 19. The electrocardiogram was divided into (1) normal, (2) incomplete right bundle branch block, (3) right ventricular dominance without widespread inversion of T waves and (4) with inversion of T waves.

There was no symptomatic deterioration in most of these patients in the first three decades. Four of 10 with symptoms had progressive dyspnea. Neither increased heart size, nor electrocardiographic changes were seen in 28. Four of five with Grade 4 tracings showed increasing degrees of right ventricular dominance. Subacute bacterial endocarditis occurred three times in two patients.

There usually was no symptomatic, radiologic or cardiographic deterioration. Symptomatic deterioration occurred in four and cardiographic, but not symptomatic, deterioration occurred in two. Therefore, at present there seems to be little indication for operation in those patients who show no real evidence of right heart stress.

SOLOFF

Cathcart, E. S. and Williams, I. T. D.: The Effect of Head-Down Position on the Excretion of Certain Urinary Constituents. Clin. Sc. **41:** 121, (Feb.), 1955.

It has been postulated that there may be an intracranial receptor which plays a role in regulating fluid volume. Changes in water and sodium excretion are known to occur when the posture is changed from recumbent to upright. The authors sought to study the effects of the head-down position, which may be assumed to cause changes in renal and intracranial venous pressures opposite to those seen on standing.

Seven subjects, free of renal dysfunction, were studied. The head-down position was achieved by raising the foot of the bed 12 degrees. There was no significant change in excretion of water, chloride, total mols (M) or creatinine.

ENSELBERG

PHYSIOLOGY

Donald, K. W., Bishop, J. M., Cumming, G. and Wade, O. L.: The Effect of Exercise on the Cardiac Output and Circulatory Dynamics of Normal Subjects. Clin. Sc. **41:** 37 (Feb.), 1955.

Compared with the very great number of observations on patients with heart disease studied by cardiac catheterization, there is a remarkable paucity of data on normal subjects. The authors therefore studied the cardiorespiratory response to exercise of 16 healthy subjects.

The most striking finding was that the oxygen uptake, the A-V oxygen difference and the cardiac output achieved a steady state after the first minute of exercise in all but one subject. A minute after cessation of exercise, these values returned to a steady state close to the pre-exercise levels in all but four subjects who had performed the heaviest exercise. The ventilation remained elevated for a longer period.

There was a linear relationship between cardiac output and oxygen uptake over the range of exercise studied. Contrary to some other published reports, the authors found a rise in pulmonary arterial pressure in all subjects but one. The increases varied from 3 to 33 mm. Hg, in the latter subject reaching a level of 52 mm. Hg. Pulmonary arterial pressures fell rapidly upon cessation of exercise after returning to the resting levels within two minutes. The pulmonary arterial resistance did not change significantly, and the work of the right ventricle was found to rise roughly in proportion to the severity of exercise performed.

ENSELBERG

Cooper,. K E. and Kerslake, D. McK.: Changes in Heart Rate During Exposure of the Skin to Radiant Heat. Clin. Sc. **41:** 125 (Feb.), 1955.

The effects on heart rate were studied in subjects in whom a large area of skin was warmed by radiant heat. A rise in heart rate was noted within eight seconds after starting the heat. The oral temperature fell in the first ten minutes and then rose slowly. There was no significant blood pressure alteration. The increase in heart rate began a few seconds before peripheral vasodilatation commenced. Furthermore, the rise in heart rate in response to heating the legs was unchanged when the leg circulation was arrested. The authors believe that the rise in heart rate begins as a result of a change in the pattern of nervous impulses from the heated area. The rise in heart rate seems to be determined by the rise in skin temperature.

ENSELBERG

Odeblad, E.: Electromagnetic Measurement of the Blood Streaming Velocity in Man. Acta med. scandinav., **151:** 95 (Feb. 23), 1955.

The author reviews the theoretical considerations concerned with the application of an electromagnetic flowmeter to clinical practice. The major parts of the flowmeter are a magnet, platinum or silver electrodes, an amplifier and a recorder. Using this technic the author found the blood streaming velocity in the umbilical cord of the newborn infant to be 2.3 ml. per second per Kg. of fetal body weight in one case and 2.6 ml. per second per Kg. body weight in a second case. The blood flow in the radial artery of an adult was found to be 1.2 ml. per second when the hand was placed in cold water and 2.1 ml. per second when the hand was placed in warm water.

ROSENBAUM

Billings, H. H. and Brown, E. B., Jr.: Effect of Splenectomy on Changes in Plasma and Blood Volume Produced by Inhalation of 30 and 40 Per Cent CO_2 in Dogs. Am. J. Physiol. **180:** 363, (Feb.), 1955.

Dogs were anesthetized with Pentothal. Under this anesthetic hematocrit, cell count and hemoglobin increased within 15 minutes on 30 per cent carbon dioxide. Despite the fact that this concentration of carbon dioxide in the inspired air was maintained for two hours, these changes persisted. A return to control values was not achieved 45 minutes after the high carbon dioxide was discontinued. Plasma volume was slightly reduced and blood volume increased during carbon dioxide breathing. Splenectomy prevents the rise in hematocrit and blood volume. A loss in circulating blood volume is not a factor in the immediate posthypercapnic hypotension in dogs.

OPPENHEIMER

Siebens, A. A., Smith, R. E. and Storey, C. F.: Effect of Hypoxia on Pulmonary Vessels in Man. Am. J. Physiol. **180:** 428 (Feb.), 1955.

Under normal conditions, exercise was observed to be associated with an increased blood oxygen content and flow, a small rise in pulmonary artery pressure but a fall in pulmonary vascular resistance. However, during hypoxia, when exercise was achieved to such a level so that no further increase of oxygen use or flow resulted, then there was a further rise in pressure and an increase in resistance. This indicates pulmonary vasoconstriction.

OPPENHEIMER

Greisheimer, E. M., Ellis, D. W., Stewart, G., Webber, D. L., Makarenko, L., Thompson, K. T., Resinski, M. G. and Frankenburg, W. K.: Cardiac Output by Cuvette Oximeter Under Cyclopropane-Oxygen and Ether Anesthesia. Am. J. Physiol. **180:** 357 (Feb.), 1955.

The cuvette oximeter lends itself to determination of cardiac output under various types of anesthetic agents. Anesthetized dogs were studied.

The present report includes the results found under cyclopropane-oxygen anesthesia and under the combination of the above with ether. It presents, in addition, a tentative method for the determination of the concentrations of cyclopropane and ether in blood, in the presence of each other. This method of analysis is adaptable to both experimental and clinical studies.

Of 76 determinations of cardiac output by cuvette oximeter on 14 dogs, 37 were done under cyclopropane-oxygen anesthesia alone and 39 under combined cyclopropane-oxygen ether anesthesia. The concentration of cyclopropane in arterial blood was determined in the former and the concentrations of both cyclopropane and ether were determined in the latter.

The cardiac output increased slightly during cyclopropane-oxygen anesthesia alone, as reported previously. Although the cardiac output was slightly higher under combined anesthesia than under cyclopropane-oxygen alone, it did not show the same tendency to increase as under ether alone. In other

words, cyclopropane may have a "steadying" effect on cardiac output, when ether is present, as indicated under the conditions existing in these experiments. Heart rate and stroke volume were both slightly higher under combined anesthesia than under cyclopropane-oxygen alone, but still not as high as found under ether alone. Systolic, diastolic and mean blood pressures were all lower under combined anesthesia than under cyclopropane-oxygen alone. The peripheral resistance began to decrease under cyclopropane-oxygen and continued to decrease throughout the experiment. The decrease under cyclopropane is in contrast to our previous findings.

OPPENHEIMER

Harris, W. H. and Sonnenblick, E. H.: A Study of Calcium and Magnesium in the Cerebrospinal Fluid. Yale J. Biol. & Med. **27:** 297, (Feb.), 1955.

Of the 15 metal ions found in central nervous system tissue, only four are consistently found in cerebrospinal fluid. These are sodium, potassium, magnesium and calcium. The role of the latter two ions in various metabolic functions of the central nervous system is being actively studied. Since some evidence implies that cerebrospinal fluid closely resembles the interstitial fluid bathing the cells of the central nervous system, determinations of the calcium and magnesium content in cerebrospinal fluid were made.

The calcium content in normal subjects was found to be 4.95 ± 0.11 mg. per cent and of magnesium, 3.01 ± 0.06 mg. per cent. An interesting finding was the remarkable constancy of the Ca^{++}: Mg^{++} ratio in normal subjects, 1.64 ± 0.03. In view of the fact that calcium and magnesium are mutually antagonistic, and that magnesium is associated with high metabolic activity and high energy production systems, it appears that the central nervous system requirement for these ions differs from other body systems and that their ratio is under rigid control by some highly selective mechanism.

ENSELBERG

McKinley, W. P.: Paper Electrophoresis of Steroid Derivatives. Science **121:** 139 (Jan. 28), 1955.

A technic is presented by which individual steroids in mixtures can be identified by paper electrophoresis. The hydrazones of estrogens, androgens and progesterone have different electric mobilities in a sodium borate solvent. This method is considered superior to partition chromatography because mixtures have one component present in a much higher concentration than others.

WAIFE

Miller, H. C. and Behrle, F. C.: The Effects of Hypoxia on the Respiration of Newborn Infants. Pediatrics **14:** 93 (Aug.), 1954.

The effects of administering atmospheres containing 10 and 12 per cent oxygen to healthy newborn infants of different ages are reported. Infants under 24 hours of age tended to hypoventilate throughout the period of hypoxia. Infants, six to 11 days old, hyperventilated for the first 2 or 3 minutes and then showed a decrease, although not as marked as observed in the infants under 24 hours of age. Infants 16 to 48 days of age, showed the most marked increase in ventilation, but even in these infants it was poorly maintained as compared to responses seen in adults.

Hypoxia produced a slowing of the respiratory rate in all infants except the very oldest. Tidal air was increased at first and then decreased. The increases in tidal air accounted for most of the increase in minute volume seen in the older infants. Hypoxia increased the incidence of periodic breathing in the two older groups of infants, but had very little effect on infants under 24 hours of age.

It is suggested that the relative inability to induce periodic breathing in infants under 24 hours of age, as compared to those several weeks old, is further evidence indicating that metabolism of the medullary respiratory centers is to a larger extent anaerobic than at the later periods of postnatal life.

BERNSTEIN

Handley, C. A. and Moyer, J. H.: Significance of the GFR/TmC Ratio. Am. J. Physiol. **180:** 151 (Jan.), 1955.

The ratio between glomerular filtration rate and the tubular maximum for glucose was observed to remain constant, despite the fact that many procedures and drugs which change each of them were used in these experiments. This was interpreted to mean that there have been changes in the number of active nephrons. In a small number of cases in human beings, a similar phenomenon is suggested.

OPPENHEIMER

Markus, G. and Feigen, G. A.: Early Disappearance of T-1824 From the Circulation of Rabbits. Am. J. Physiol. **180:** 115 (Jan.), 1955.

When T-1824 leaves the circulation in rabbits, the disappearance rate during the first 28 minutes is logarithmic. One and five mg. doses behave in a similar fashion. The mean ratio between the optical densities at 16 and 4 minutes is 0.843, standard error of the mean ±0.004, standard deviation of the distribution ±0.036. Extrapolation to zero revealed a loss of 20 per cent during the first 16 minutes.

OPPENHEIMER

Garb, S., Penna, M. and Scriabine, A.: Species Differences in the Utilization of Glucose for Contractile Force by Isolated Perfused Hearts. Am. J. Physiol. **180:** 103 (Jan.), 1955.

The test objects were isolated perfused mammalian hearts. Species differences were marked when

he action of glucose on the force of cardiac contraction was studied. In cases where the substrate was depleted, the rat's heart was observed to have a 50 per cent increase in the force of contraction when glucose was added. Responses from hearts of other species were less. In the guinea pig, the increase was 12 per cent, while in the rabbit it was eight per cent, but in the cat it was only four per cent.

OPPENHEIMER

Garb, S. and Scriabine, A.: Relationship of Temperature to the Utilization of Glucose for Contractile Force by Cat Heart Muscle. Am. J. Physiol. **180:** 101 (Jan.), 1955.

The contractile force of isolated cat papillary muscles was tested. When the glucose concentration was 200 mg. per cent at 37 C., there was a small increase in contractile force. However, when these same concentrations were observed at a temperature 10 C. lower, the effects were a much more marked increase in contractile force. These results emphasize the fact that temperature must be considered, when the effects of various substrates are studied for their action on the isolated mammalian myocardium.

OPPENHEIMER

DiPalma, J. R.: Latency of Isolated Cat Atrium and Its Possible Relationship to Fibrillation. Am. J. Physiol. **180:** 96 (Jan.), 1955.

At low temperatures in intact cats, there was a greater susceptibility to fibrillation. It is pointed out that this may be explained by the loss of latency which exists at low temperatures.

OPPENHEIMER

Leeds, F. H., Freeman, N. E., Gilfillan, R. S., and Coelho, H. M.: Blood Pressure in Minute Vessels of Human Skin. Arch. Surg. **70:** 25 (Jan.), 1955.

The blood pressure in the small cutaneous vessels of the skin was studied in a series of 83 sympathectomized lower extremities, using the method of elevation and reactive hyperemia. In 72 per cent of cases, the readings were definitely increased as compared with preoperative results. The response was most marked in patients with exaggerated vasomotor tone and no arterial obliteration. In the group with occlusive arterial vascular disease, the patients with small artery obstruction demonstrated a greater change following sympathectomy than those with large artery occlusion.

ABRAMSON

Atlas, L. N.: Clinical Observations on Vasosensory Innervation of Lower Extremity. Arch. Surg. **70:** 17 (Jan.), 1955.

The author present several case reports to illustrate the various types of pain associated with occlusive arterial vascular disorders and the means that are available for their control. The results were used in the elucidation of the mechanisms responsible for the pain.

The theory was presented that vasosensory neurons from the lower limb course along the iliac arteries and abdominal aorta, reaching and entering the spinal cord via the lumbar sympathetic ganglia. Other peripheral vasosensory neurons may leave the preaortic plexus by way of its connections with the celiac ganglion. By traversing this ganglion and the splanchnic nerves, along with other visceral afferents, they enter the spinal cord at various levels within the thorax.

ABRAMSON

Mirsky, I. A.: Secretion of Antidiuretic Hormone in Response to Noxious Stimuli. Arch. Neurol. and Psychiat. **73:** 135 (Feb.), 1955.

Verney and co-workers have shown that noxious stimuli in animal or man result in an inhibition of diuresis induced by water ingestion. Stimuli which can initiate the "alarm reaction," elicit an antidiuretic response. Hypothalamic extracts of stressed animals exhibit a marked decrease in the concentration of antidiuretic hormone.

A procedure for the assay of antidiuretic substances in blood plasma was used to determine the activity of the plasma of animals and man exposed to noxious stimuli. Pain produced a mild electric shock, noise, produced by a Federal Siren, intraperitoneal injection of 1 mg. of histamine hydrochloride per 100 Gm. of body weight and the emotional stimuli of a strange environment for more than two minutes caused an elevation of the plasma antidiuretic titer in rats. Adrenalectomy, treatment with cortisone or hypophysectomy did not interfere with these reactions. Adrenalectomized and hypophysectomized rats produce a higher antidiuretic titer in response to noxious stimuli than controls. These results indicate that neither the adrenal gland, anterior or posterior pituitary is essential for the release of antidiuretic substance into the circulation.

Ischemic pain in men caused an increase in their plasma antidiuretic titer. Surgical operations in men also produced this increase, which disappeared in 2 to 3 hours. Subtler, stressful situations also produced this increase.

These results reveal that an antidiuretic substance is released into the circulation when the organism is exposed to a situation which has noxious significance. This substance behaves like the antidiuretic hormone. Since it is released in hypophysectomized animals, the antidiuretic hormone must take origin in some extrahypophyseal site. The hypothalamus is suggested as a posible site.

WECHSLER

Catchpole, B. N. and Jepson, R. P.: Hand and Finger Blood Flow. Clin. Sc. **41:** 109 (Feb.), 1955.

The authors describe a method of plethysmography incorporating a means of shutting off all finger blood flow and employing copper-tellurium heat-flow discs. They felt that artefact distortion was eliminated and that the method made it possible to estimate blood flow in all of the finger tissue. At temperatures from 15 to 30 C., the blood flow through the fingers exceeded that through the hand, but the proportion fell at higher temperatures. The heat-flow recordings consistently followed the plethysmographic readings, but no correlation was attempted. The heat-flow discs are useful especially when simultaneous records are desired.

ENSELBERG

Guyton, A. C., Lindsey, A. W. and Kaufmann, B. N.: Effect of Mean Circulatory Filling Pressure and Other Peripheral Circulatory Factors on Cardiac Output. Am. J. Physiol. **180:** 463 (March), 1955.

Venous return is approximately proportional to mean circulatory filling pressure minus pressure in the right atrium. This pressure gradient also dilates vessels and thus facilitates venous return. As a result, the cardiac output increases, more than would be predicted, as the venous pressure rises. Mean circulatory filling pressure is the upper limit for right atrial pressure. Changes in arterial and arteriolar resistance affect venous return much less than changes in venular and venous resistances. Of other effective factors, it was noted that venous return is approximately inversely proportional to blood viscosity. Only if all the peripheral resistances and capacitances are held constant is venous return proportional to arterial pressure.

OPPENHEIMER

Allbaugh, E. and Horvath, S. M.: Effect of Total Occlusion of Thoracic Aorta on Blood Pressure, Splanchnic Blood Flow and Metabolic State in Dogs. Am. J. Physiol. **180:** 451 (March), 1955.

When the thoracic aorta was completely shut off, a level of the fourth interspace arterial pressure declined to 16 mm. Hg below the obstruction. Arterial pressure was greatly increased above this occlusion. While the obstruction was allowed to persist, the estimated splanchnic blood flow was reduced by 73 per cent. Although splanchnic oxygen use was less despressed, the arteriovenous oxygen difference was increased. Control values were quickly achieved in all parameters, when the obstruction was removed.

OPPENHEIMER

RHEUMATIC FEVER AND RHEUMATIC HEART DISEASE

Tillett, W. S., Johnson, A. J. and McCarty, W. R.: The Intravenous Infusion of the Streptococcal Fibrinolytic Principle (Streptokinase) into Patients. J. Clin. Invest. **34:** 169 (Feb.), 1955.

When streptokinase (as contained in Varidase) is injected intravenously by continuous or intermittent infusion, there occur certain hematologic changes. Among these are polymorphonuclear leucocytosis and irregular alterations in platelet count. No significant changes in clotting or bleeding time were seen.

Patients who showed low titers of naturally occurring inhibitor had a moderate prolongation of prothrombin time, when active fibrinolysis developed. These subjects also had a decrease in fibrinogen, plasminogen and complement. Pyrogenic reactions were present and could be controlled by antihistamines. Hypotension was also seen.

Repeated infusions had a "booster" effect, in that fibrinolytic activity was of greater degree and duration, when the same total amount of streptokinase was administered in two or three infusions, several hours apart.

WAIFE

Debré, R., Mozziconacci, P. and Nouille, J. Diagnostic Elements of Bouilland's Disease. Arch. mal coeur **48:** 76 (Jan.), 1955.

Eighty-one cases of acute rheumatic fever were analyzed to determine the incidence of cardiac complications, the development of valvular deformities and the predictability of such an evolution. Among 71 hospitalized cases, some cardiac pathology was pre-existent in six. In the remaining 65 cases, it developed during observation, in 56 per cent within the first two weeks and in 44 per cent later. In nine of these cases, there was initially no sign which would permit anticipation of cardiac involvement. The latter should be suspected whenever there were previous attacks of rheumatic fever, frequent streptococcus infections of the throat, a high sedimentation rate and a fibrinogen titer of over 8 Gm.

In order to gain information concerning the prognosis, the cases were divided into two groups according to the presence or absence of the following findings designated as "important": a sedimentation rate of 90 mm., fibrinogen over 8 Gm. a red blood count of less than 3.5 million and a white blood count exceeding 15,000 with polynuclears of over 80 per cent. The study revealed that in the presence of these "important" signs, the chances are that one out of two cases will take a serious course. In the absence of the laboratory findings, the outlook is in general favorable, but a serious evolution is possible. The authors conclude that every case of acute rheumatic fever requires energetic treatment, regardless of laboratory findings.

PICK

Deglaud, L. and Laurens, P.: Vectorcardiographic Study on Right Heart Strain in Mitral Stenosis. Arch. mal coeur **48:** 129 (Feb.), 1955.

A vectorcardiographic study is presented of 118 cases with pure or predominant mitral stenosis, in

14 before and subsequent to commissurotomy. Four types of vectorcardiograms are described as reflecting the degree of right ventricular preponderance. The distinction of these four patterns is based on the degree of deviations of the frontal QRS loop, the contour and width of the QRS loop in the horizontal plane and the direction of the horizontal T loop. Ordinarily, there is a good correlation between these different types of vector loops and the extent of elevation of the pulmonary arterial pressure. If a discrepancy is found, an additional valvular lesion, either aortic or mitral insufficiency, must be suspected.

Surgery, followed by clinical and hemodynamic improvement, is invariably reflected in the vectorcardiogram by regression in the degree of alterations. This amelioration is, according to the authors, more obvious in the vectorcardiogram than in the scalar electrocardiogram. Comparison of pre- and postoperative vectorcardiograms and a study of alterations, occurring in the direction and contour of its different portions, permits an understanding of variations of the electric field as caused by right heart strain.

PICK

Balaguer-Vintro, I., Torner-Soler, M. and Gibert-Queralto, J.: Comparative Study of Methods used for Measurements of Mitral Stenosis. Acta cardiol. **10:** 44, (Fasc. 1), 1955.

A comparative study was made in 15 cases of mitral stenosis by determining the following data: the mitral area according to Gorlin's formula, the mean pulmonary arterial wedge pressure, the mitral resistance index, determined according to Werkö, and a formula developed by the authors. In general, there was good correlation between the results determined by these various methods. In certain cases calculations taking into account the variations of the diastolic period (Gorlin's formula and the diastolic mitral resistance index, according to the authors), gives more accurate information.

From the practical standpoint, determination of the mean pulmonary arterial wedge pressure by itself gives an idea of the approximate degree of reduction of the mitral area. Gorlin's formula has the advantage that its accuracy can be checked at surgery or at autopsy. In the material of the authors, this could be verified during commissurotomy in seven cases and postmortem in four cases.

PICK

Davies, L. G., Goodwin, J. F. and Van Leuven, B. D.: The Nature of Pulmonary Hypertension in Mitral Stenosis. Brit. Heart J. **16:** 440 (Oct.), 1954.

The effect of hexamethonium bromide on the pulmonary circulation was studied in nine individuals with mitral stenosis, three with predominant mitral incompetence and two with additional significant aortic disease.

In four with marked pulmonary hypertension, significant falls in pulmonary artery pressure, amounting to 30 to 40 per cent of the resting level, occurred without significant diminution of cardiac output. Lesser degrees of falls occurred in those with slight to moderate pulmonary hypertension. Pulmonary wedge pressure measured in two also showed falls.

The fall of the pulmonary artery pressure without a fall in cardiac output suggests that hexamethonium reduces pulmonary vascular resistance by producing pulmonary artery dilatation. This effect of the drug may be of value in the treatment of individuals with pulmonary hypertension who are not suitable for valvotomy.

SOLOFF

Chancey, R. L., Morris, A. J., Conner, R. H., Catanzaro, F. J., Chamovitz, R. and Rammelkamp, C. H., gr.: Studies of Streptococcal Prophylaxis. Comparison of Oral Penicillin and Benzathine Penicillin. Am. J. M. Sc. **229:** 165 (Feb.), 1955.

A comparison is presented, showing the effectiveness of oral and Benzathine penicillin in prophylaxis against streptococcal infections and also the incidence of toxic reactions caused by each drug. A single, intramuscular injection of the benzathine preparation was given in a dose of 1,200,000 and 600,000 units to 960 and 950 adult males, respectively. Oral penicillin doses of 250,000 units twice daily were given to 845 men for 10 days. The incidence of reactions resulting from the prophylactic treatment was 5.2, 2.1, and 1.07 per cent. The reactions were mild and were characterized chiefly by urticarial type of skin lesions. All three programs were effective in eliminating the carrier state for group A streptococci. The larger dose of benzathine penicillin was the most effective regimen; new acquisitions of the streptococcus occurred less frequently in this group. From these data it would appear that intramuscularly benzathine penicillin is an effective agent for prophylactic use and avoids the problem of failure of the patient to take the drug, when given orally. Because of the incidence of reactions to the depot preparation, further experience with smaller doses is advisable.

SHUMAN

Manchester, B., Scotti, T. M., Reynolds, M. L. and Dawson, W. H.: Aschoff Bodies in Left Auricular Appendages of Patients with Mitral Stenosis. Arch. of Int. Med. **95:** 231 (Feb.), 1955.

The records of 35 patients operated upon for mitral stenosis have been reviewed. The biopsy specimens of the left atrial appendages were examined and Aschoff bodies were noted in 13 (37 per cent). Clinical and laboratory methods are inadequate for the detection of active subclinical rheumatic carditis. The postoperative mortality

and morbidity, as well as clinical improvement, were the same for the group of cases in which biopsy was positive for Aschoff bodies and the group in which it was negative. Statistically, reactivation of rheumatic fever probably occurred with equal frequency in the two groups.

BERNSTEIN

Evans, M. and Parker, R. A.: Honeycomb Lung and Mitral Stenosis in Scleroderma. Thorax **9:** 158 (June), 1954.

A case of scleroderma (acrosclerotic type) with honeycomb lung and mitral stenosis is described. The cysts in the lung were thought to be caused by contraction of the fibrous tissue of the lung parenchyma. The fibrous tissue may be the end result of a sclerodermatous or chronic inflammatory process. The finding of mitral stenosis in this case of scleroderma is probably fortuitous.

BERNSTEIN

Catanzaro, F. J., Brock, L., Chamovitz, R., Perry, W. D., Siegel, A. C., Stetson, C. A., Rammelkamp, C. H., Jr., Houser, H. B., Stolzer, B. L., Wannamaker, L. W. and Hahn, E. O.: Effect of Oxytetracycline Therapy of Streptococcal Sore Throat on the Incidence of Acute Rheumatic Fever. Ann. Int. Med. **42:** 345 (Feb.), 1955.

The results of treatment of 506 patients with streptococcal exudative pharyngitis, with oxytetracycline administered for five days, is presented. Serving as controls, 480 patients received no specific therapy. In the dosages employed, oxytetracycline reduced the convalescent streptococcal carrier rate 55 per cent as compared to the control group. In addition, the average antistreptolysin response in the treated patients was 49 per cent less than that observed in the control patients. Maximal inhibition of antibody production occurred in the treated patients in whom the infecting organism was eliminated. Recurrent pharyngitis occurred more frequently in the treated group, particularly in those patients who remained carriers. The second clinical illness usually developed within 2 to 3 weeks after therapy had been discontinued. Suppurative complications were of infrequent occurrence in both groups. Rheumatic fever developed within 35 days after the onset of the streptococcal infection in 12 patients in the control group and in five patients in the group treated with oxytetracycline. The attack rate was reduced, therefore, from 2.94 per cent in the control group to 0.99 per cent by therapy with oxytetracycline ($p = 0.07$). Until further data are available, it is recommended that penicillin, administered so that effective concentrations are maintained for at least 10 days, be used in the treatment of streptococcal infections. This may be accomplished by the single injection of 600,000 to 900,000 units of benzathine penicillin or by the oral administration of 250,000 to 500,000 units of penicillin, twice daily for 10 days. Erythromycin, chlortetracycline and oxytetracycline should be reserved for those patients who are unable to tolerate penicillin and, if they are employed, should be administered for at least 10 days.

WENDKOS

Fowler, N. O., Noble, W. J., Giarratano, S. J. and Mannix, E. P.: The Clinical Estimation of Pulmonary Hypertension Accompanying Mitral Stenosis. Am. Heart J. **49:** 237 (Feb.), 1955.

Forty patients, having rheumatic heart disease and mitral stenosis, were studied clinically and by cardiac venous catheterization in an attempt to develop clinical criteria for the estimation of the degree of pulmonary hypertension. The patients were divided into three groups according to the mean pulmonary arterial blood pressure: mild or no pulmonary hypertension, below 30 mm. Hg; moderate pulmonary hypertension, 30 to 49 mm. Hg and severe pulmonary hypertension, above 50 mm. Hg. Eighteen subjects were in the mild group, 10 were moderate and 12 were severe.

The following criteria were found helpful in indicating moderate or severe pulmonary hypertension: (1) roentgenologic evidence of right ventricular hypertrophy; (2) precordial lead V_1 of the electrocardiogram; (3) evidence of right heart failure and (4) pulmonary edema. The following criteria were of little or no help: (1) the height of the "A" wave of the right atrial pulse pressure; (2) the intensity of the apical diastolic murmur; (3) the intensity of the pulmonic second sound and (4) hemoptysis.

RINZLER

ROENTGENOLOGY

Van der Straeten, P. P.: Postmortem Coronarography in Aged Persons. Acta cardiol. **10:** 15 (Fasc. 1), 1955.

The author reports the results of postmortem roentgenography of the heart in 34 aged human subjects, before and after injection of the coronary vascular bed by lipiodol. Two types of degenerative changes could be distinguished. The first type which is always present and intensified with age, consists in widening of the large arteries and opening of collaterals of middle and small caliber. This condition is considered to represent a part of the physiologic alterations associated with aging. The second alteration, found commonly but not as often as the first, consists in reduction of the lumen of the large coronary arteries, either localized or more extensive, with production of atheromatous plaques and califications. Such areas of coronary stenosis may ultimately progress to complete obstruction of the vessel. In many cases, a striking discrepancy was noted between the pronounced stenosis of large coronary arteries and the degree of development of collateral channels.

PICK

BOOK REVIEWS

Digital Plethysmography. *George E. Burch.* New York, Grune and Stratton, 1954, 142 pages, 83 illustrations. Price $5.00.

The inability to express adequacy of blood flow in quantitative terms is one of the major unresolved problems in experimental and clinical peripheral vascular physiology. The pulse wave of a digit may, under certain circumstances, serve as an index of the rate of blood flow. This relationship of pulse wave to blood flow may be expressed plethysmographically by the venous occlusion technic in which veins draining a part are obstructed and the rate at which blood accumulates in the part from the arterial side is measured. The pitfalls inherent in most attempts to measure blood flow rates by venous occlusion are reviewed critically and in detail in this monograph. With a clear knowledge of the limitations of the technic, the author describes a new plethysmographic method for recording continuously, during a pulse cycle, the rate of blood flow into and out of the digit of man. The author believes the technic is standardized sufficiently to be applied to the study of normal and abnormal physiologic vascular states of the fingertip of man.

This excellent monograph should be most helpful to those investigators who use plethysmography in the study of the peripheral circulation.

STANFORD WESSLER, M.D.

Coronary Heart Disease in Young Adults. A Multidisciplinary Study. *Menard M. Gertler and Paul D. White.* Cambridge, Harvard University Press, 1954, 218 pages illustrated. Price $5.00.

This interesting volume is the result of an exhaustive study of a group of 100 ambulatory patients with a history of myocardial infarction at least six months earlier, who at the time of infarction ranged in age from 22 years through 40 years. Ninety-seven were men and three women. There were 146 unmatched controls and a group of matched controls for the 97 male patients, consisting of 74 men from the unmatched control group and 23 additional men.

The clinical findings were not impressive. The use of alcohol or tobacco could not be implicated as an etiologic factor. Heredity seemed to be important, but the mode of gene transference or inheritance and the degree of penetrance were not clarified. Of particular interest was the study of morphologic characteristics, endomorphic mesomorphs predominating. This part of the study was most complete. Athletic ratings were higher and the incidence of managerial occupations greater in the coronary group. The coronary patients were less masculine in their final scores than the matched control group. Endocrine studies limited to a thyroid and a testicular-adrenal survey based on 24-hour urinary sterone excretion were inconclusive. Mean total cholesterol levels in the serum were higher in the coronary group, but a threshold level for coronary heart disease could not be said to exist. An important additional factor appeared to be the serum phospholipids and their relation as a colloidal stabilizer of the serum cholesterol. The phospholipids showed an increase with age in the normal group but did not keep pace with age in the coronary group. The serum uric acid was found to be higher in the coronary patients. The increased levels of cholesterol were highest in the mesomorphs, the increased uric acid in the endomorphs. As to diet, the controls ingested more cholesterol than the coronary patients. A study of the oxidation-reduction potentials of saliva showed a faster rate of change per minute in the coronary patients during the entire test procedure.

Although on the whole there were suggestive differences between the coronary and control groups, no conclusions of a fundamental nature were possible.

WALLACE M. YATER, M.D.

The Digital Circulation. *Milton Mendlowitz.* New York, Grune & Stratton, 1954. 192 pages, 115 illustrations, 12 in color, 31 tables. Price $6.75.

Although the title of this book might suggest that a very specialized subject is discussed, this is not really so. Most patients who go on to amputation as the result of arterial occlusive disease do so because of gangrene of toes. Furthermore, vasospastic phenomena are most severe in the fingers. The digital circulation, therefore, is the area of involvement in peripheral vascular diseases that is not only most important to study but happens to be a most accessible area of the body for measuring blood flow.

The author's interest in measuring blood flow and blood pressure in clubbed fingers initiated a large number of investigations on digital blood flow in various conditions which finally led the author to put his experience and also a great deal of collateral information into this book. The discussion of the anatomy, physiology, pharmacology and pathology of the circulation in the hand and foot served as an excellent review to this reviewer. The chapter on methods of measuring blood flow in the digits is based on the author's extensive personal experience and should be of value to anyone who is considering the use of one or more of these methods or is already using them. Capillaroscopy is discussed as well as the measurement of blood flow by skin temperature studies, plethysmography, oscillometry and calorimetric methods. The latter is described in con-

siderable detail. Digital vascular resistance and the effect of intravascular blood viscosity are also given full treatment. Finally, oxygen exchange is discussed as a more recent development in studying digital blood flow. The peripheral vascular diseases are discussed in a chapter of twenty-one pages. This is a considerable condensation but does contain some useful information relating digital blood flow to various phenomena in each disease discussed. Clubbing of the fingers receives extended treatment as would be expected from the author's background. It was Mendlowitz who demonstrated that acquired symmetric clubbing of the fingers and toes is usually associated with an increase in blood flow in the fingers. The author discusses in some detail the various clinical conditions that may result in local over-supply of blood to the digits with the production of clubbing. Special mention should be made of tables 3 and 4 which summarize the effects of drugs on the autonomic system.

This book is a valuable supplement to the larger clinical books on peripheral vascular diseases. It stresses basic physiologic principles which give insight into clinical phenomena in this field. One minor criticism is the small type used in the reference numbers of the bibliography at the end of the volume. These numbers are too small to be seen easily and reduce the value of this otherwise considerable and useful list of references.

MEYER NAIDE, M.D.

Selected Papers of Dr. Frank N. Wilson. *Franklin D. Johnston and Eugene Lepeschkin, Eds.* Ann Arbor, Edwards Brothers, Inc., 1954. 1090 pages, 489 figures, 61 tables. Price $10.00.

Many colleagues and students of the late Dr. Frank N. Wilson were aware that his collected raticles on electrocardiography comprised an authoritative text and urged him to compile them into a treatise, but were informed that he felt unable to spare the time. His many publications in medical journals have been readily available only to the few physicians with easy access to medical libraries and the very few who were fortunate enough to obtain reprints. Those familiar with the electrocardiographic literature have drawn upon Dr. Wilson's contributions freely and have applied his fundamental studies widely in the clinical field.

In selecting Dr. Wilson's outstanding papers and reproducing them in a single volume, Doctors Franklin Johnston and Eugene Lepeschkin have performed a greatly needed service. The collection and organization of Dr. Wilson's papers has provided an invaluable reference and text for the entire profession and the comments by his associates have injected deep human interest. The reproduction of the many electrocardiograms and line drawings in this volume is excellent and like that in the original articles.

This volume includes Wilson's fundamental studies on direct and semidirect leads that have led to the universal adoption of multiple precordial and unipolar limb leads and the use of the central terminal as the indifferent electrode. The original studies elucidating bundle branch block in animals, the series on experimental myocardial infarction and the monumental articles on clinical application, published more than one to two decades ago and again accessible in this volume, still constitute the basis of modern electrocardiography. The work has been confirmed and elaborated but still remains essentially unchallenged.

This volume also includes the pioneer studies from the Wilson Heart Station from which the concept of ventricular gradient has developed and the studies which initiated the subspecialty of vectorcardiography.

The *Selected Papers of Dr. Frank N. Wilson* is an essential part of the library of every cardiologist.

GORDON B. MYERS, M.D.

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.

Telephone Gramercy 7-9170

LAUNCH CONTROLLED RHEUMATIC FEVER PREVENTION STUDY

Inauguration of a study designed to establish criteria for streptococcal control in the school population as the basis for community rheumatic fever prevention programs all over the nation has been announced by the Association. The study, which will involve participation of 2,900 children in three Philadelphia elementary schools, is being conducted by the Heart Association of Southeastern Pennsylvania in cooperation with the national Association and local groups.

The study is designed to fill important gaps in knowledge about control of streptoccal infections. Earlier studies in a military population have demonstrated the efficacy of prompt and adequate penicillin treatment of streptococcal infections in preventing initial rheumatic fever attacks.

The Philadelphia study is the nation's first controlled effort of its kind designed to yield information on the behavior of the streptococci in causing infections that may be followed by rheumatic fever. This information will provide a basis for determining the most effective and most practical methods for controlling streptococcal infections in a school population. Among the streptococcal diagnostic procedures that will be evaluated is the use of throat cultures.

The study will continue for at least one year. A report on the results will be made after a sufficient time has been allowed for followup and a careful review of the findings.

Director of the study is John P. Hubbard, M.D., Professor of Preventive Medicine at the University of Pennsylvania Medical School, who is assisted by David Cornfield, M.D., of the Department of Preventive Medicine and Pediatrics in the same school.

The plan for the controlled study was drawn up by the Heart Association of Southeastern Pennsylvania, in conjunction with the medical division of the Board of Education and the Department of Public Health and Preventive Medicine of the School of Medicine, University of Pennsylvania. It was approved by a joint committee of the American Heart Association's Council on Rheumatic Fever and Congenital Heart Disease and Council on Community Service and Education. The study is supported financially by the American Heart Association, the Heart Association of Southeastern Pennsylvania, the Einstein-Godek Children's Fund of Philadelphia, and E. R. Squibb and Sons and Wyeth, Inc., pharmaceutical firms which also are supplying free penicillin for the pilot program.

"CARDIAC-IN-AGRICULTURE" STUDY STARTED IN IOWA

The first program of its type in the United States, designed to help cardiac farmers continue to lead productive lives, has been inaugurated by the national Association in cooperation with the Iowa Heart Association.

The one-year pilot study is being conducted among farmers of Washington County, Iowa. Objective of the Iowa project will be to determine the physical capacity of farmers with heart diseases, and to help them, through medical and social counseling, to remain active within their physical limitations. If possible, the farmers will be helped to remain in agriculture. It is hoped that the findings of this study will provide a pattern for similar projects throughout rural America.

L. E. January, M.D., Professor of Internal Medicine at the State University of Iowa College of Medicine, has accepted appointment as responsible investigator for the study.

The Iowa project represents an extension of the Association's "Cardiac-in-Industry" program into the field of agriculture. As a part of this program, work classification units have been established during the past few years in urban centers to assist factory workers, office personnel and professionals who have cardiovascular ailments.

Cooperating with the Heart Associations in

the Iowa study will be the College of Medicine of the State University of Iowa; the Extension Service of the Division of Agriculture, Iowa State College; the Division of Vocational Rehabilitation; the Washington County Medical Society; the Heart Committee of the Washington County Tuberculosis and Health Association; the Washington County Health Unit; the Iowa Farm Bureau Federation; the Washington County Farm Bureau; and the Washington Evening Journal. The Iowa State Medical Society has approved the project.

GOLD HEART AWARDS

Three Gold Heart Awards for outstanding contributions to cardiovascular medicine and to the heart disease program were presented at the American Heart Association Annual Dinner in New Orleans, October 23. The Association's highest honor was bestowed on Thomas M. McMillan, M.D., Philadelphia, Frederick K. Trask, Jr., Cos Cob, Connecticut, and posthumously to T. Duckett Jones, M.D.

In the Gold Heart Award scrolls, Dr. McMillan is cited for "distinguished editorship of *Circulation* since its inception in 1950," and, prior to that, for his editorship of *The American Heart Journal*. His efforts are described as having "won acceptance and recognition from scientists and physicians throughout the world for the American Heart Association and its program of professional education."

Dr. McMillan is Professor of Clinical Medicine at the University of Pennsylvania School of Medicine. He is retiring as editor-in-chief of *Circulation* on December 31.

At the time of his death in November, 1954, Dr. Jones was regarded as one of the world's leading authorities on rheumatic fever and rheumatic heart disease. A former Vice Chairman of the Association and Chairman of its Council on Rheumatic Fever and Congenital Heart Disease, he served until his death as Vice President and Medical Director of the Helen Hay Whitney Foundation, New York, which supports research in the rheumatic fever field. The Gold Heart citation described Dr. Jones' life as one of "dedication, attainment and service to humanity." It referred to him as a "teacher, scientist and physician . . . world-renowned for his contributions to the understanding and treatment of rheumatic fever."

The third Gold Heart recipient, Mr. Trask, recently retired after five years as Chairman of the Association's Finance Committee. His citation paid tribute to "his practical wisdom and guidance in shaping policy (which) are truly reflected iu the security of the heart program, and in the trust and confidence inspired by the American Heart Association's stewardship of public funds."

NEW OFFICERS OF ASSOCIATION AND COUNCILS AND SECTIONS

Irvine H. Page, M.D., Cleveland, has assumed his duties as President of the American Heart Association. Dr. Page succeeded E. Cowles Andrus, M.D., Baltimore, as chief executive of the Association at the Annual Meeting and Scientific Sessions in New Orleans where other officers of the Association, its Sections and Councils were elected. As retiring President, Dr. Andrus will automatically become Chairman of the Scientific Council.

Edgar V. Allen, M.D., Rochester, Minn. was chosen as President-elect. The following were elected as Vice Presidents of the Association: William H. Bunn, M.D., Youngstown, Ohio; S. DeWitt Clough, Chicago; Mrs. Preston Davie, New York; Eugene B. Ferris, M.D., Atlanta; Louis E. Martin, M.D., Los Angeles; A. W. Robertson, Pittsburgh; David D. Rutstein, M.D., Boston; and Robert W. Wilkins, M.D., Boston. Berkeley D. Johnson of New York was elected as Treasurer.

The Association's Councils and Sections held business meetings in New Orleans during which they chose the following officers:

Scientific Council: E. Cowles Andrus, M.D., Baltimore, Chairman; Eugene A. Stead, M.D., Durham, N. C., Vice Chairman.

Council on Community Service and Education: Martin Cherkasky, M.D., New York, Chairman; Ray E. Trussel, M.D., New York, Vice Chairman.

Council on Rheumatic Fever and Congenital Heart Disease: Maclyn McCarty, M.D., New York, Chairman; George Wheatley, M.D., New York, Vice Chairman.

Section on Basic Science: William F. Hamilton, M.D., Augusta, Ga., Chairman; Louis N. Katz, M.D., Chicago, Vice Chairman.

Section on Circulation: Arthur J. Merrill, M.D., Atlanta, Chairman; E. A. Hines, M.D., Rochester, Minn., Vice Chairman.

Section on Clinical Cardiology: Emmet B. Bay, M.D., Chicago, Chairman; William P. Thompson, M.D., Los Angeles, Vice Chairman.

Section on Cardiovascular Surgery: Frank Glenn, M.D., New York, Chairman; Robert Gross, M.D., Boston, Vice Chairman.

Officers of the Council for High Blood Pressure Research were scheduled for election at the Council's Annual Meeting in Cleveland, November 18–19.

GENERAL MARK CLARK ACCEPTS HEART FUND CHAIRMANSHIP

In accepting the National Chairmanship of the 1956 Heart Fund Campaign, General Mark W. Clark emphasized today that the only nationwide fund raising effort of the American Heart Association and its affiliates will be conducted in the month of February, 1956.

General Clark stated:

"The illness of President Eisenhower has brought into sharp focus the magnitude of the threat of the heart diseases to the health of this country.

"It is our earnest hope that the American people will give their fullest support to the Heart Fund Campaign, thus making possible a vast acceleration of the efforts of medical science to find the unknown causes of the heart diseases, as well as to bring the benefits of heart research to people everywhere.

"During the past five years, more than 13,000,000 Heart Fund dollars have been channeled into heart research. The objective of the 1956 campaign will be to secure greatly expanded research support as well as to further education and community heart programs of the Association."

This will be the third successive year as National Chairman for General Clark, former Commander-in-Chief in the Far East, and now President of the Citadel, the Military College of South Carolina at Charleston.

CIRCULATION RESEARCH NAMES ASSOCIATE EDITOR

Harold Feil, M.D., Cleveland, will become Associate Editor of Circulation Research, the Association's bimonthly journal of fundamental studies, on January 1. Dr. Feil, Clinical Professor of Medicine at Western Reserve University, will work in conjunction with Carl J. Wiggers, M.D., the journal's editor-in-chief. Dr. Feil is former President of the Cleveland Area Heart Society.

To Use Interlingua

Also on January 1, *Circulation Research* will appear for the first time in an expanded form. In order to accommodate the greatly increased volume of worthy manuscripts, the publication will increase its number of pages in each issue by approximately one-fourth. At the same time, *Circulation Research* will inaugurate a policy of publishing summaries of its articles in Interlingua, the international language which has proved so helpful in making the contents of *Circulation* more readily available to non-English-speaking physicians and scientists.

DR. SCHUYLER JOINS ASSOCIATION AS ASSISTANT MEDICAL DIRECTOR

Leonard H. Schuyler, M.D., New York, has been appointed as an Assistant Medical Director of the Association. He will aid in the administration of the research support and professional education programs.

Dr. Schuyler, a graduate of the Duke University Medical School, formerly was a Research Fellow in medicine at the Vascular Research Laboratory of the New York Hospital-Cornell University Medical School.

NAME WINIFRED DEVLIN AS NURSING CONSULTANT

Miss Winifred Devlin, R.N. has been appointed as Consultant Nurse in Cardiovascular Diseases for the newly-established Cardiovascular Nursing Advisory Service, a joint project of the Association and the National League for Nursing.

Miss Devlin, former Industrial Nurse Consultant in the U. S. Public Health Service, will assist Heart Associations throughout the

country in establishing closer relations with the nursing profession and in providing special educational services for nurses.

RESEARCH INFORMATION EXCHANGE NEEDS DATA FROM INVESTIGATORS

The Bio-Sciences Information Exchange is seeking to complete its record of research being conducted throughout the United States by obtaining information from scientists working without grants or other financial support from outside agencies.

The Information Exchange, originally created and supported by governmental agencies which support scientific research, serves as a clearing house for information about current research in the biological, medical and psychological sciences. Many voluntary health agencies, including the American Heart Association, and private foundations cooperate with the Exchange.

A detailed subject index on research in progress is maintained by the Exchange. This information is available without cost to cooperating agencies and to investigators associated with recognized research institutions. In this way, agencies or investigators can learn about work in their field on which published reports are not yet available. Individual investigators are not given information on the amounts of grants to others, nor may they use any prepublication material for publication or publication references.

Scientists working on projects without outside support are urged to write to Dr. Stella Leche Deignan, Director, Bio-Sciences Information Exchange, 1113 DuPont Circle Building, Washington 6, D. C.

AMERICAN COLLEGE OF CHEST PHYSICIANS

An award of $500 is being offered by the Committee on Cardiovascular Research of the American College of Chest Physicians for the "best manuscript on 'Acute Pulmonary Edema' " submitted before May 1, 1956.

Eligibility is restricted to unpublished manuscripts or those published after April 1, 1955. The manuscript must be based on an original study of either an experimental or clinical type, and it may include problems of therapy.

Additional information may be obtained from Aldo A. Luisada, M.D., Chairman, Section on Cardiovascular Physiology, American College of Chest Physicians, 112 Chestnut Street, Chicago 11, Ill.

MEETINGS CALENDAR

Dec. 11–16: Radiological Society of North America, Chicago, D. S. Childs, 713 E. Genesee St., Syracuse, N. Y.

Dec. 13: American Academy of Obstetrics and Gynecology, Chicago. C. Paul Hodgkinson, 116 S. Michigan Blvd., Chicago 3.

Jan. 20: Southern Section, American Federation for Clinical Research, New Orleans. John H. Moyer, M.D., Baylor University College of Medicine, 1200 M. D. Anderson Blvd., Houston.

Jan. 25: Western Section, American Federation for Clinical Research, Carmel, Calif. B. H. Scribner, M.D., Veterans Administration Hospital, Seattle 8, Wash.

Feb. 6–8: American Academy of Allergy, St. Louis, Francis C. Lowell, 65 E. Newton St., Boston.

Feb. 10–11: American College of Radiology, Chicago. W. C. Stronach, 20 N. Wacker Drive, Chicago 6.

March 24–25: American Psychosomatic Society, Sheraton Plaza Hotel, Boston. Abstracts must be submitted by Dec. 1 to Stanley Cobb, M.D., 551 Madison Avenue, New York 22.

ABROAD

Jan. 20–27: Pan-American Congress of Gastro-Enterology, Havana. Dr. Norberto E. Stapler, 1667 J.E. Uriburu, Buenos Aires.

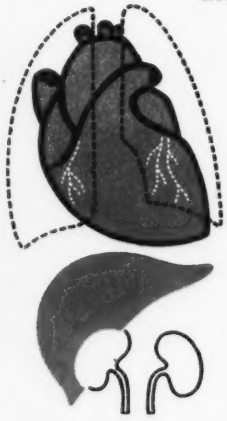
Jan. 22: French Assembly of General Medicine, 53rd Medical Meeting, Paris. Dr. Guy Godlewski, 157 Avenue Malakoff, Paris 16e.

March 6–9: Ciba Foundation Symposium on Influence of Ionizing Radiation on Cell Metabolism (by invitation), London. Dr. G. E. W. Wolstenholme, Director of Foundation, 41 Portland Place, London W. 1.

March 26–28: Ciba Foundation Symposium on The Biophysics and Biochemistry of Viruses (by invitation), London. Dr. G. E. W. Wolstenholme, Director of Foundation, 41 Portland Place, London, W. 1.

does your diuretic cause acidosis?

know your diuretic



diuresis without depletion of alkaline reserve—avoiding dangers of acid-base imbalance—is characteristic of the organomercurials. In contrast, the diuretic activity of carbonic anhydrase inhibitors, acidifying salts, and the resins depends on production of acidosis.

TABLET

NEOHYDRIN®

BRAND OF CHLORMERODRIN

(10.2 MG. OF 3-CHLOROMERCURI-2-METHOXY-PROPYLUREA IN EACH TABLET)

- action not dependent on production of acidosis
- no "rest" periods... no refractoriness

a standard for initial control of severe failure

MERCUHYDRIN®

BRAND OF MERALLURIDE INJECTION SODIUM

Leadership in diuretic research

Lakeside LABORATORIES, INC., MILWAUKEE 1, WISCONSIN

8875B

Circulation

DECEMBER 1955
VOL. XII NO. 6

OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

CONTENTS

INDEX ISSUE